

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61B 5/00</b>		(11) International Publication Number: <b>WO 97/01986</b>
<b>A1</b>		(43) International Publication Date: 23 January 1997 (23.01.97)
<p>(21) International Application Number: PCT/US96/11435</p> <p>(22) International Filing Date: 8 July 1996 (08.07.96)</p> <p>(30) Priority Data: 08/500,388 6 July 1995 (06.07.95) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 08/500,388 (CIP) Filed on 6 July 1995 (06.07.95)</p> <p>(71) Applicant (for all designated States except US): THOMAS JEFFERSON UNIVERSITY [US/US]; 1020 Locust Street, Philadelphia, PA 19107-6799 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): JOSEPH, Jeffrey, I. [US/US]; 1335 June Lane, Penn Valley, PA 19072 (US). SUN, Xiaoguang [US/US]; 516 Valleywyck Drive, King of Prussia, PA 19406 (US).</p> <p>(74) Agent: LAVORGNA, Gregory, J.; Seidel, Gonda, Lavorgna &amp; Monaco, P.C., Suite 1800, Two Penn Center Plaza, Philadelphia, PA 19102 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i></p>
<p>(54) Title: IMPLANTABLE SENSOR AND SYSTEM FOR MEASUREMENT AND CONTROL OF BLOOD CONSTITUENT LEVELS</p>		
<p>(57) Abstract</p> <p>This invention is an implantable sensor and system capable of measuring, controlling, monitoring and reporting blood constituent levels. The implantable sensor (14) for sensing in vivo the level of at least one blood constituent in mammalian vascular tissue (20, 24) having at least one source of radiation from infrared through visible light, arranged to direct the radiation at the tissue where it is affected by interaction with the tissue, and at least one detector. The invention also encompasses a device for measuring and controlling the level of a blood constituent, such as glucose or oxygen, and includes an implantable infrared source and sensor module for generating an output signal representative of the sensed infrared radiation. The system includes a processor module responsive to the output signal which performs spectral analysis of the output signal and generates a control signal. The system further includes other devices for dispensing (16) doses of medications or controlling organ function in response to the control signal.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

**IMPLANTABLE SENSOR AND SYSTEM FOR MEASUREMENT  
AND CONTROL OF BLOOD CONSTITUENT LEVELS**

**Field of the Invention**

The present invention relates to medical devices for sensing the  
5 level of a constituent in a body fluid such as blood, including but not limited to  
blood glucose, oxygen, antibiotics, enzymes, hormones, tumor markers, fatty  
acids, and amino acid levels. The present invention also relates to a system for  
control, monitoring and reporting blood constituent levels in response to sensed  
levels and to provide continuous monitoring and control of blood constituent  
10 levels to permit aggressive therapy and concomitant clinical benefit of such  
therapy.

**Background of the Invention**

Metabolic processes in living organisms proceed according to an  
exact administration of chemical compounds that are manufactured and released  
15 throughout the organism. These chemical compounds control the function as  
well as the condition of vital organs, tissues and processes that sustain or exist  
within the organism. In many instances these chemical compounds can be  
found in the organisms fluids including blood as in the case of mammals. These  
chemical compounds in the blood are generically referred to as blood constitu-  
20 ents.

- 2 -

Blood Constituents*Glucose*

A blood constituent such as Glucose is an important nutrient and indicator for human organisms. During periods of moderate to heavy exercise, the muscles utilize large amounts of glucose to release energy. In addition, large amounts of glucose are taken up by muscle cells in the few hours after a meal. This glucose is stored in the form of muscle glycogen, and can later be used by the muscles for short periods of extreme use and to provide spurts of energy for a few minutes at a time. Moreover, glucose is an essential nutrient for brain and spinal cord function. Glucose is the only nutrient that can normally be utilized by the brain, retina, and germinal epithelium of the gonads in sufficient quantity to supply those organs with their required energy. Brain tissue has an obligate requirement for a steady supply of blood glucose. When blood glucose levels fall below 50 *mg/dl*, memory loss, agitation, confusion, irritability, sweating, tachycardia, and hypertension commonly occur. Brain failure occurs when blood glucose levels fall below 30 *mg/dl*, and is associated with coma, hypoventilation, and vascular instability. Death may occur. Therefore, it is important to maintain the blood glucose concentration at a high enough level to provide this necessary nutrition.

At the same time, however, it is also important that the blood glucose concentration not rise too high. Glucose exerts a large osmotic pressure in the extracellular fluid. If glucose concentration rises to excessive levels, this can draw water out of the cells and cause considerable cellular dehydration. Blood sugars above 200 *mg/dl* often exceed renal threshold producing an osmotic diuresis by the kidneys, which can deplete the body of fluids and electrolytes.

The steady supply of blood glucose is tightly controlled by the pancreas and the liver. Following a meal, gastric digestion and intestinal absorption provide an increasing amount of carbohydrates, free fatty acids, and amino acids into the portal venous blood. Sixty percent of the glucose absorbed after a meal is immediately stored in the liver in the form of glycogen. Be-

- 3 -

tween meals, when the glucose concentration begins to fall, liver glycogen is dephosphorolated, allowing large quantities of glucose to diffuse out of the liver cells and into the blood stream. The liver, a large organ, can store six percent of its mass as glycogen. In contrast, muscle tissue can store only two percent  
5 of its mass as glycogen, barely enough to be used by the muscle as its own energy reserve.

Normally, blood glucose concentration is regulated by two hormones, insulin and glucagon, secreted by the pancreas. Insulin is released in a bimodal fashion from the pancreas in direct response to a rise in blood glucose  
10 level and, to a lesser extent, to a rise in the blood level of free fatty acids and amino acids. Insulin promotes transport of these nutrients into the cells to be utilized for energy, to be stored as glycogen or triglycerides, or to be synthesized into more complex compounds such as proteins.

Some individuals develop diabetes mellitus, and do not secrete  
15 insulin in sufficient quantities to properly regulate blood glucose. Lack of insulin inhibits the cell membrane transport of nutrients such as glucose, fatty acids, and amino acids into the cells, forcing the cells to use other compounds for energy and cell growth. Diabetics exhibit a decreased utilization of those nutrients by the cells, resulting in a marked increase in blood glucose concentration, an increase in triglyceride mobilization from the adipose tissue resulting  
20 in a marked increase in blood fatty acid and cholesterol concentrations, and a marked loss of protein on a cellular level. Many of the severe end-organ complications which result from diabetes are due to the cellular wasting which occurs secondary to abnormal amino acid uptake and protein wasting. Abnormal fatty acid metabolism results in elevated levels of blood concentrations of  
25 low-density lipoprotein (LDL), cholesterol, and free fatty acids, all leading to accelerated atherosclerosis and obstructive vascular disease. Those with diabetes are also prone to ketosis, and develop dehydration, acidosis, and electrolyte imbalance under stress. In some forms of the disease, insulin injections may  
30 be required, and other long-term complications such as retinopathy, blindness and kidney disease commonly occur.

- 4 -

The pancreas also secretes glucagon, a hormone which has cellular functions that are diametrically opposed to those of insulin. Glucagon stimulates the liver to release large amounts of glucose from glycogen when the blood glucose concentration falls below 90 *mg/dl*. This system of insulin inhibition and glycogen release prevents glucose concentrations from falling dangerously low.

In short, glucose is regulated within a narrow range between 80 and 90 *mg/dl* during fasting, with a rise toward 140 *mg/dl* following a high carbohydrate meal. The liver functions as a reservoir and buffer, so that glucose is available to the brain during meals and during periods of prolonged fast.

Type I diabetics have an absolute deficiency in insulin synthesis by the beta cells of the pancreas, and have the most severe clinical course if not aggressively managed with nutrition and insulin therapy. These individuals are ketosis prone and may develop a severe metabolic acidosis. Wide swings in blood glucose commonly occur with a high incidence of symptomatic hypoglycemia following insulin therapy. End organ dysfunction is common due to accelerated atherosclerosis, cellular protein wasting, and small vessel disease.

Type II diabetics release insulin from the pancreas in a blunted fashion following the intake of food. Blood insulin levels do not rise sufficiently to prevent hyperglycemia. However, in some forms of the disease, insulin levels may be elevated. In addition, peripheral tissues of type II diabetics may possess a smaller number of membrane tissue receptors and possibly a down regulation of those receptors. Ketoacidosis is uncommon. However, hyperglycemia and hyperosmolar conditions may occur, leading to coma and death. Insulin therapy may or may not be required to maintain normal glycemia levels. Other therapies include weight loss, diet, and oral hypoglycemic agents which stimulate the pancreas to release larger quantities of insulin.

There is no doubt that long term tight glucose control is able to significantly reduce the incidence of end organ complications. Control of blood glucose concentration in diabetic individuals by Q.I.D. insulin injections has, of course, been done for many years. This type of treatment does have a

- 5 -

number of serious drawbacks, however. One or more needle sticks of the finger must be performed on a daily basis to obtain blood for glucose assay. Many patients suffer anxiety and discomfort when subjected to finger pricking. After the blood sample is obtained, the sample must be exposed to a surface  
5 coated with chemical agents and enzymes that produce a color change corresponding to glucose concentration. The patient or medical practitioner performing the assay must interpret the color change accurately, and inject a dose of insulin based on the glucose level. Some patients use a hand held glucometer to measure glucose concentrations in their blood. Many individuals experience  
10 anxiety and discomfort when facing injections, and resist them. Some individuals may have no one to administer the required injections, but have difficulty injecting themselves. Dosage can also be problematic. Color change can be misinterpreted, and it is not unusual for patients to miss an injection, or to be off schedule. In addition, patients even have difficulties when using  
15 glucometers. Syringes, which these days tend to be disposable, contribute to the growing problem of hazardous medical waste.

Some of these problems have been partially dealt with in the past, but none of the past attempts at dealing with these problems has been entirely satisfactory. Non-invasive optical techniques for measuring blood glucose have  
20 been developed, but these techniques do not solve the problems associated with administering insulin injections where required. Non-invasive optical techniques for measuring blood glucose are prone to error because the interface between the sensor and the tissue changes constantly with manipulation and contact pressure. Skin and extremity blood flow also varies considerably with cardiac  
25 output, body temperature and level of activity. These non-invasive optical techniques typically use a source of infrared (IR) radiation and a detector to measure absorption, reflection, or some other parameter to derive information about blood glucose levels. The effective optical distance from the IR source and the detector changes with subcutaneous body fat and the variability in placing the  
30 sensor from day to day. In addition, non-invasive IR sensors measure blood glucose in a non-continuous manner, and are thereby limited to functioning as

- 6 -

a glucose measuring device and not as a therapeutic device for the treatment of diabetes.

Implantable pumps for administering insulin as well as other chemical compounds are known. It has even been proposed to automatically  
5 measure blood glucose and administer insulin as may be required using an implantable sensor and insulin pump system. The latter systems are known to incorporate sensors to perform chemical analysis of blood samples which require the introduction of chemical reagents into the patient's body. Typically, these reagents periodically need to be replenished, which imposes the require-  
10 ment of access below the surface of the skin through which fresh reagents must be injected from time to time. No matter what sensor is used, insulin still must be injected approximately every 6 weeks into the pump reservoir by placing a thin needle through the skin. Moreover, commercially available implantable pumps have FDA approval only for the infusion of chemotherapy and Baclofen  
15 for the treatment of spastic leg disorders. Pumps implanted for the infusion of insulin have been successfully tested in humans, however, there is no clinical benefit to implantations without a sensor for closed-loop control.

### *Oxygen*

Cells require a continuous supply of oxygen and nutrients for  
20 basic metabolism. Oxygen must be efficiently absorbed through the lungs and combined with hemoglobin in the blood for proper transport to the tissues. Oxygen delivery depends upon the pumping action of the heart (blood flow per minute) and the content of oxygen bound to hemoglobin and dissolved within the plasma.

25 Once in the tissues, oxygen is released from the hemoglobin molecule and diffuses through the interstitial fluid and into each cell. The workhorse of any mammalian cell is the mitochondria. A series of surface bound enzymes within the mitochondria transfer electrons generated during the metabolism of glucose called the Krebs' Cycle. Oxygen acts as the final  
30 electron acceptor generating \_\_\_\_\_ATP, \_\_\_\_\_NADH heat, and



- 7 -

carbon dioxide as a waste product. High energy phosphate compounds such as ATP and NADH are generated to provide energy for most cellular metabolic processes. Examples of processes requiring ATP for energy include: maintaining ionic gradients, active membrane transport, intracellular synthesis, and cell reproduction. Highly metabolic tissues such as brain and heart muscle tolerate an inadequate delivery of oxygen and other nutrients poorly. Conditions that produce a low blood flow state include cardiac pump failure, hemorrhage, dehydration, and sepsis. The tissues attempt to compensate for this low blood flow state by extracting a greater portion of the delivered nutrients.

When oxygen delivery is insufficient to supply the aerobic needs for ATP production, alternative metabolic pathways will dominate causing lactic acid to accumulate. Anaerobic metabolism produces an insufficient supply of high energy compounds and cellular functions quickly deteriorate. Ionic gradients are lost and repair mechanisms cease to function. Persistent low flow states lead to ischemic damage to various end-organs including the kidneys, brain, and liver. Hypoxemia and metabolic acidosis proceeds organ failure followed by death of the mammal.

Large multicellular organisms require a distribution system for the delivery of oxygen and nutrients. The heart, blood vessels, and hemoglobin molecules efficiently transport oxygen and other nutrients to the peripheral tissues such that every cell is within diffusion distance of a nutrient capillary. Typically, the heart provides pulsatile blood flow (cardiac output) exceeding 5.0 liters per minute. During periods of increased metabolic activity such as exercise, infection, or following surgery, the cardiovascular system is required to increase the cardiac output several fold to meet the increased oxygen requirements. Many disease states compromise the cardiovascular system such that an inadequate supply of oxygen and nutrients reach the tissues. Chronic heart failure due to hypertension, ischemic heart disease, valve disease, or alcohol is the most common cause of death in the U.S.

- 8 -

Fatigue, shortness of breath, and poor exercise tolerance are common as the failing heart is unable to pump sufficient quantities of blood to satisfy the metabolic needs of the tissues. In addition, cardiac arrhythmia may further compromising forward blood flow. To solve some of these problems, physicians are can only intervene with medications and supplemental oxygen improving oxygenation and blood flow to the vital organs.

*Devices and Implantable Sensors for Detection of Blood Constituents*

Devices for the detection of blood glucose incorporate an implantable sensor using a semipermeable membrane and an enzyme coated surface and an oxygen electrode have been studied for the continuous measurement of blood glucose. This sensor has significant drift and quickly fails due to host reaction and contamination of the membrane and enzyme surface. Needle-type amperometric glucose sensors implanted within the subcutaneous tissues and having an enzyme coated surface and an electrical output to an external processor are known, but loss of sensitivity and sensor drift occur upon implantation. This type of sensor, which is in the form of a thin wire, must be inserted through a hollow needle into the subcutaneous tissue and must be changed every three to four days due to enzyme depletion and membrane contamination. In addition, glucose concentration within the subcutaneous tissues lags 20 minutes behind blood glucose and varies between 70-80% of blood values.

Devices for the detection of blood oxygen such as a pulse oximeter are well known. The oximeter measures blood oxygen by measuring the amount of light absorbed by hemoglobin at two different frequencies. It was observed that oxygenated hemoglobin absorbs light differently from that of reduced hemoglobin at two certain frequencies. For example, at 660 nanometers, reduced hemoglobin is known to absorb as much as ten times the amount of light as oxygenated hemoglobin, whereas oxygenated hemoglobin absorbs a much greater amount of light at the infrared wavelength of 940

- 9 -

nanometers. In addition, the absorbed light has a pulsatile sinusoidal component caused by pulsing volumes of arterial blood from the heart.

The typical pulse oximeter has two light emitting diodes (LEDs) and a detecting sensor arranged in a noninvasive manner to allow emitted light to pass through body tissue for detection by the sensor. As the light passes through the body tissue it is partially absorbed as described above and then detected to produce an estimate of blood oxygen in the human body.

Pulse oximeters have been developed for continuous measurement of in-vivo human blood oxygen saturation by transilluminating tissue noninvasively. However, these devices have several disadvantages. Because the pulse oximeter is external to the body and noninvasive, it can only measure red and infrared light transmitted through blood in human tissue, typically the ear or finger. As a consequence, several inaccuracies are introduced into the measurement of oxygenated hemoglobin by the absorption and dispersion of light through intervening tissues such as skin, soft tissue, bone, venous blood and arterial blood. In addition, the sensors of a pulse oximeter are susceptible to interference from ambient light, low perfusion, and body motion. Pulse oximetry is known in the art and further described in Kevin K. Tremper and Steven J. Barker, "Pulse Oximetry", *Anesthesiology*, Vol 70, pp 70-108 1989 which is incorporated herein by reference.

Therefore there is a need to control levels of blood constituents, such as glucose concentration, oxygen, fatty acid concentration, and amino acid concentration without requiring blood sampling, chemical test reagents or reagent injections, and with continuous monitoring of levels of blood constituents. The present invention meets that need by providing a sensor which is fully implantable and can be used In-vivo, can be used continuously and over the long term, and which is reliable and safe.

The present invention provides the ability to achieve close, continuous monitoring and control of blood constituents such as, but not limited to, glucose and oxygen, as well as tumor markers, antibiotics, enzymes,

- 10 -

hormones, fatty acids, and amino acid levels, thereby providing a clinical and therapeutic breakthrough.

### Summary of the Invention

5 The present invention is an implantable sensor and system capable of measuring, controlling, monitoring, and reporting blood constituent levels. The invention includes an implantable device for sensing In-vivo the level of at least one blood constituent in mammalian vascular tissue. The internal device includes a communication system and a calibration system.

10 In one aspect of the invention, the implantable device comprises at least one source of radiation from infrared through visible light, arranged to direct the radiation at the tissue. The radiation is affected by interaction with the tissue and detected by a plurality of detectors. The detectors are located with respect to the tissue to receive radiation affected by said tissue. The detectors each have a filter transparent to a discrete narrow band of radiation.  
15 Each detector provides an output signal representative of detected radiation in said narrow band.

In another aspect of the invention, the implantable device comprises at least two sources of radiation from infrared through visible light, arranged to direct the radiation at the tissue. The radiation is affected by  
20 interaction with the tissue and detected by at least one detector. The detectors being located with respect to the tissue to receive radiation affected by said tissue. Each source is adapted to emit radiation in a selected number of discrete bandwidths and each detector is adapted to detect the radiation being emitted in the discrete bandwidth. Each detector provides an output signal representative  
25 of detected radiation in said discrete bandwidth.

In another of its aspects, the present invention includes a device for both measuring and controlling the level of a blood constituent in a mammal, and comprises an implantable infrared source and sensor module for directing infrared radiation through vascular tissue such as, but not limited to, an  
30 artery, a vein, a vascular membrane, or vascular tissue. The sensor module

- 11 -

senses the infrared radiation after it has passed through the tissue and generates an output signal representative of the sensed infrared radiation. A processor module, responsive to the output signal from the infrared source and sensor module, performs spectral analysis of the output signal and derives therefrom  
5 a control signal representative of the level of the blood constituent. The processor module or another device in communication with the processor module is used to control, monitor, and report the level of the blood constituent.

In one aspect of the invention, an insulin pump is used to control the level of glucose by dispensing doses of insulin in response to the control  
10 signal. In another aspect of the invention, an implanted cardiac pacemaker as well as an internal cardiac defibrillator (ICD) is used to control the level of oxygenated hemoglobin in the blood in response to the control signal. In yet another aspect of the invention, an implanted dispensing device is used to control the level and administration of medications such as, but not limited to,  
15 cardiac drugs, antibiotics, or chemotherapies in response to the control signal. In still another aspect of the invention, the level of tumor markers is monitored and reported to other devices in response to the control signal. In all aspects of the invention, the system is capable of monitoring and reporting all blood constituents that are sensed and measured.

20 In another aspect of the invention, an implantable oxygenation, hemoglobin, and perfusion sensor is provided to obtain frequent objective data on patients with chronic illnesses such as heart failure and respiratory failure. Patients would be monitored for changes in hemoglobin oxygen saturation (pulse oximeter), hemoglobin concentration (infrared measurement), and changes in  
25 tissue perfusion (analysis of the photoplethysmograph waveform) for the purpose of detecting cardiovascular decompensation early so that the physician can manage the problem as an outpatient. Visits to the emergency room and admissions to the ICU would significantly diminish. Data from the sensors will be stored within a memory chip and Physicians would be notified automatically  
30 if data changed significantly from data established for an individual patient's background.

- 12 -

Typically, cardiovascular patients are not alerted to significant cardiovascular decompensation until overt symptoms have occurred resulting in the need for acute care in a n ICU following admission through an emergency room. With this implantable sensor of the present invention, physicians will be able to detect early cardiovascular decompensation and institute corrective therapy as required.

Data stored in a memory by the invention can provide the patient or clinician, either directly or remotely, with the natural history of the disease process. The physician will be able to administer medical therapy based on an objective presentation of data and conclude from the data and immediately acquire information on the effects of the therapy applied. The invention provides the major determinants of oxygen delivery such as \_\_\_\_\_ to the tissues which are measured by the sensor.

For example, after a patient is stabilized following a myocardial infarction and the onset of heart failure and pulmonary edema, a sensor would be implanted under local anesthesia. The sensor would immediately provide and collect data directly and communicate data to an extracorporeal device for remote monitoring of the patient for changes in oxygenation, perfusion, hemoglobin concentration, and cardiac arrhythmia. Once discharged from the hospital, the sensor would continue to monitor the patient and provide data extracorporeally for significant changes in oxygenation, perfusion, hemoglobin concentration, and cardiac arrhythmia. Depending on the condition of the patient, data would be stored in a memory or reported directly to the patient or medical personnel for interpretation as required. Therefore, the present invention can facilitate the administration of medications, appropriately according to objective measured data thereby improving cardiac contractility and improved tissue blood flow in advance of an acute event.

In another aspect of the invention, the implantable device comprises at least one radiation source consisting of at least two discrete spectral bands lying somewhere within the infrared through visible spectrum, arranged to direct the radiation at the tissue. The radiation is affected by

- 13 -

interaction with the tissue and detected by at least one detector. The different spectral bands in each source are substantially collinear and interact with substantially identical tissue. The detectors being located with respect to the tissue to receive radiation from source affected by said tissue.

5 Discrimination amongst different spectral bands is provided by each spectral band having a unique temporal or frequency modulation. Each detector provides an output signal representative of detected radiation from said source. A communication means is provided to relay the output signal from detector to processor. A processor is used to determine level of blood  
10 constituent in blood.

#### Description of the Drawings

For the purpose of illustrating the invention, there is shown in the drawings a form which is presently preferred; it being understood, however, that this invention is not limited to the precise arrangements and instrumentalities shown.  
15

Figure 1 illustrates an implantable glucose sensor according to one embodiment of the invention as it might be implanted in a human patient, shown in conjunction with an implantable insulin pump, with the sensor array arranged to monitor blood flow through a blood vessel.

20 Figure 2 is an enlarged view of the sensor of Figure 1, showing the sensor in conjunction with an implantable insulin pump and processor module containing associated processing and control electronics.

Figure 3 is a transverse sectional view through the sensor shown in Figure 2, taken along the lines 3-3 in Figure 2, showing the distribution of  
25 individual photocells.

Figure 4 is a longitudinal sectional view through the sensor, taken along the lines 4-4 in Figure 3.

Figure 5 illustrates an implantable glucose sensor according to an alternate embodiment of the invention as it might be implanted in a human

- 14 -

patient, with a sensor array arranged to monitor blood flow through a vascular membrane such as parietal peritoneum.

Figure 6 is an enlarged view of the embodiment of the sensor of Figure 5, showing the sensor in conjunction with an implantable insulin pump and processor module containing associated processing and control electronics.

Figure 7 is a sectional view through the sensor shown in Figure 6, taken along the lines 7-7 in Figure 6.

Figure 8 is a top plan view of the sensor shown in Figure 6, showing the distribution of individual photocells.

Figure 9 illustrates a third embodiment of the invention, partially broken away, showing an arrangement of individual photocells in a rectangular array.

Figure 10 is a sectional view of the sensor shown in Figure 9, taken along the lines 10-10 in Figure 9.

Figure 11 is an enlarged plan view of an individual photocell from the array shown in Figure 9.

Figure 12 is a fourth embodiment of the invention, in cross-sectional view.

Figure 13a illustrates a functional block diagram of an implantable blood constituent sensor module with communication means shown in conjunction with extracorporeal receiving, calibration, and communication modules.

Figure 13b illustrates a typical oxygen delivery process monitored according to a preferred embodiment of the present invention.

Figure 13c illustrates an implantable oxygen sensor module having at least one pair of detector and sensor elements according to a preferred embodiment of the present invention.

Figure 13d illustrates a plethysmograph of a plurality of pulse waves through a vascular membrane at a specific rate as would be measured by at least two pairs of the detector and sensor elements shown in Figure 13c.



- 15 -

Figure 14 is a schematic representation of a device for controlling the blood oxygen according to a preferred embodiment of the present invention.

Figure 15a is a schematic representation of a device for controlling the level of blood oxygen according to another preferred  
5 embodiment of the present invention.

Figure 15b is a schematic representation of vascular tissue plethysmography and ECG fibrillation according to a preferred embodiment of the present invention.

Figure 16a is a schematic representation of an infrared sensor  
10 according to a preferred embodiment of the present invention.

Figure 16b is a schematic representation of the infrared sensor shown in Figure 16a used to measure and control a medicinal blood constituent such as an antibiotic.

Figure 17 is a schematic representation of an infrared sensor  
15 according to another preferred embodiment of the present invention.

Figure 18a is an illustration of an extracorporeal calibration and communication module unit for use in connection with implantable blood constituent sensor modules according to the invention.

Figure 18b is an illustration of a extracorporeal calibration  
20 handheld unit for use in connection with implantable blood constituent sensor modules according to the invention.

Figure 18c is a functional block diagram showing the operation of an implantable device according to the invention in communication with the extracorporeal calibration and communication module shown in Figure 18a.

25 **Description of the Invention**

Referring now to the drawings, wherein like numerals indicate like elements, there is shown in Figure 1 a representation of an implantable blood constituent monitoring and control system 10.

*Glucose Monitoring and Control System*

- 16 -

Figure 1 shows a blood glucose monitoring and control system 10 comprising a sensor and an insulin pump, as it might be surgically implanted in a patient 12. It should be understood that Figure 1 is not intended to be anatomically accurate in every detail; rather, it is intended to represent generally how the system 10 would be implanted. Moreover, it should also be understood that, while for convenience the present invention is illustrated and described in reference to monitoring and control of blood glucose, the invention is not so limited, and encompasses the monitoring and control of other blood constituents such as, by way of example and not by way of limitation, fatty acid or amino acid concentration. Several preferred embodiments of the invention are presented below.

As best seen in Figure 2, system 10 comprises a sensor assembly 14 connected to a processor/pump module 16 via a signal cable 18. Sensor assembly 14, described in greater detail below, has an opening which enables it to be arranged to substantially surround a blood vessel 20. Processor/pump module 16 is illustrated as dispensing insulin via a tube 22 into a second blood vessel such as a vein 24, which may be the portal vein for direct transport to the liver. Alternatively, processor/pump module dispenses insulin via a non-thrombogenic multilumen catheter including a one-way valve, directly into the peritoneal space adjacent the hilum of the liver. Insulin will be rapidly absorbed into the portal venous system and transported to the liver. While the processor/pump module 16 is illustrated as implanted within a patient's body, the pump portion of processor/pump module 16 may also be an external device, worn or otherwise carried by the patient, without departing from the present invention. Where an external pump is used, insulin may be delivered percutaneously into an infusaport implanted under the patient's skin for final transport to the peritoneal cavity or portal vein. Alternatively, insulin may also be delivered by an external device with a needle placed chronically within the patient's subcutaneous tissues. Moreover, when an external pump is used, the processor portion of processor/pump module 16 requires a data telemetry portion in order to telemeter command signals to the external pump. Insulin

- 17 -

reservoirs and pumps, telemetry devices, and infusaports are all known *per se*, and therefore need not be described here in any great detail.

Processor/pump module 16 contains a conventional insulin reservoir and pump. In addition to an insulin reservoir and pump, processor/pump  
5 module 16 contains an electronic microprocessor and associated electronic circuitry for generating signals to and processing signals from sensor assembly 14 and for generating control signals to the insulin pump itself. Processor/pump module 16 further includes a long-life battery to power the electronic circuitry, the sensor assembly 14 and the insulin pump.

#### 10 *Blood Constituent Sensor*

Sensor assembly 14 is illustrated in greater detail in Figures 3 and 4. Sensor assembly 14 has a body portion 26 which is generally C-shaped in transverse cross-section. Thus, body portion 26 has a longitudinal channel which runs through body portion 26, and a longitudinal gap 28 which communi-  
15 cates with the longitudinal channel. Body portion 26 is preferably fabricated from a semi-rigid material such as titanium or epoxy, which is easily worked and biocompatible for long-term implantation. The shape and semi-rigid material of sensor assembly 14 enables it to be placed closely around vessel 20 and place optical sources and individual optical detectors in optimum position with respect to vessel 20. The distance between the optical sources and the optical  
20 detectors can thus be made small and as close to constant as possible, for optimum signal acquisition.

In the embodiment of sensor 14 illustrated in Figures 3 and 4, the optical sources and optical detectors may be infrared (IR) sources and IR detec-  
25 tors, although radiation from infrared through the visible spectrum may be employed without departing from the invention. In the figures, individual IR sources and individual IR detectors are grouped together in three groups, or arrays, 30, 32, and 34. Each array comprises an IR source (30a, 32a, and 34a, respectively) and two IR detectors (30b, 30c; 32b, 32c; and 34b, 34c, respec-  
30 tively). The individual IR sources 30a, 32a, and 34a may be miniature infrared

- 18 -

diodes located, in the illustrated embodiment, on one side of vessel 20. IR sources 30a, 32a, and 34a are driven by signals generated in the processor/pump module 16 and transmitted to IR sources 30a, 32a, and 34a via conductors 36a, 38a, and 40a, respectively. Similarly, output signals from individual  
5 detectors 30b, 30c; 32b, 32c; and 34b, 34c are transmitted to processor/pump module 16 via conductors 36b, 36c; 38b, 38c; and 40b, 40c, respectively. Conductors 36, 38, and 40 collectively are dressed together to form signal cable 18, which couples sensor array 14 to processor/pump module 16. Cable 18 exits body portion through an extension portion 42, which serves to support cable 18  
10 and minimize the chance of breakage of conductors 36, 38, and 40 from flexing or being subjected to sharp bends. If desired, cable 18 may exit extension portion 42 through a strain relief sleeve 44, to further protect cable 18.

Each IR source 30a, 32a, and 34a has associated with it an optical filter 46a, 48a, and 50a, respectively. Each filter transmits a different  
15 discrete narrow band of radiation. In similar fashion, each detector 30b, 30c; 32b, 32c, and 34b, 34c has associated with it an optical filter 46b, 46c; 48b, 48c; and 50b, 50c, respectively. In this manner, each optical source and the detectors associated with it in a given array 30, 32, or 34 operates in only a discrete narrow band.

20 With this embodiment, detectors 30b, 32b, and 34b are arranged diametrically opposite IR sources 30a, 32s, and 34a, respectively, to detect light transmitted from the associated source through the blood vessel 20. The angle between the sources and the detectors is thus 180°. (These detectors could also be used to determine reflected light, since light that is not transmitted may, for  
25 purposes of the invention, be assumed to have been reflected. By determining the amount of light transmitted, and subtracting it from the amount of light emitted from the source, the amount of light reflected can be calculated.) Detectors 30c, 32c, and 34c are arranged at an angle less than 180° from the associate sources, and are located to detect IR radiation either reflected or  
30 scattered from vessel 20.

- 19 -

It is important to note that, although this embodiment of the invention is described using three arrays of IR sources and associated detectors, that precise configuration is not crucial to the invention. The invention may be implemented, for example, using a single IR source and multiple detectors for  
5 detecting reflected, scattered, and transmitted IR radiation. In such an embodiment, the IR source would not have a narrow band filter associated with it, but would emit broadband IR. Each detector, however, would have a narrow band filter associated with it, so that it would respond only to a preselected wavelength.

10 Conductors 36, collectively, 38, collectively, and 40, collectively, can be either electrical conductors or optical fibers. That is, the IR sources and the IR detectors may be located either within sensor assembly 14 itself, in which case the conductors are electrical conductors and carry electrical signals between processor/pump module 16 and sensor assembly 14, or within processor/pump  
15 module 16, in which case the conductors are optical fibers and carry infrared radiation between processor/pump module 16 and sensor assembly 14.

It will be appreciated that IR radiation generated by IR sources 30a, 32a, and 34a is directed through the walls of vessel 20, and thus the blood flowing in the vessel, to detectors 30b, 30c; 32b, 32c; and 34b, 34c located  
20 across from and at right angles to the IR sources. The IR radiation detected by the several detectors is, of course, affected by its interaction with vessel 20 and the blood flowing therethrough. Consequently, by analyzing the output signals from the several detectors, it is possible to derive information about the levels of glucose, fatty acids, and amino acids in the blood flowing through vessel 20.  
25 Preferably, although not necessarily, selected sensor/detector pairs are used for different measurement techniques. For example, pair 30a, 30b could be used to measure infrared transmittance, and pair 30a, 30c to measure infrared scattering. That is, the output signals from the several detectors can be processed differently to obtain different characteristics of the blood being measured.

- 20 -

In contrast to prior electro-chemical glucose sensors, sensor array 14 does not need require direct contact with blood, does not need to be replenished with test reagents, and can operate indefinitely.

*Alternative Blood Constituent Sensor*

5                   In another embodiment, source 30 a or 32 a, or 32 a) may consist of multiple LEDs or multiple laser diodes, each of a different wavelength spaced identically collinear or spaced very closely so that each wavelength has substantially the identical optical path and interacts with substantially identical tissue. The detector 30 b or c, 32 b or c, and 34 b or c detects light from each  
10 individual wavelength from source 30 a, 32 a, and 32 c, respectively. The processor discriminates amongst the different wavelengths by having each wavelength pulse at a different frequency or at a different time. As the processor can discriminate amongst the different wavelengths by either different frequency or temporal information, narrow wavelength filters 46 a, 48 a, and  
15 50 a are unnecessary in this embodiment. Multiple sources and multiple detectors provide redundancy or alternatively the ability to measure different chemical species, although in many cases a single source and detector is adequate. The operation of the sensor is otherwise the same as described in the previous embodiment.

- 21 -

*Vascular Membrane Sensor Interface*

An alternative form of device 10' according to the present invention is illustrated in Figures 5 through 8. In alternative form 10', the device monitors blood flowing through a highly vascular membrane, such as a portion of the parietal peritoneum 52. The parietal peritoneum is an ideal tissue for measurement due to its high vascularity, translucency, constant temperature, and brisk blood flow. As best seen in Figures 6 and 7, a portion of a vascular membrane such as the parietal peritoneum 52 (shown in phantom in Figure 6) is sandwiched between two halves 54 and 56 of an alternate form 58 of sensor assembly. Halves 54 and 56 are essentially mirror images of each other, and define a gap 60 between them, which receives the peritoneal tissue. Sensor assembly 58 is preferably molded from the same type of material as used to fabricate sensor assembly 14, as already described. The shape and semi-rigid material of sensor assembly 58 enable it to be clamped snugly around peritoneal tissue 52 and to place individual IR sources 62a through 62d and individual IR detectors 64a through 64d, 66a through 66d, 68a through 68d, and 70, in optimum position with respect to tissue 52.

One half of sensor assembly 58, such as half 56 for example, contains the individual IR sources 62a through 62e, while the other half, such as half 54, for example, contains the individual detectors 64 collectively, 66 collectively, 68 collectively, and 70. The detectors are grouped together in groups of three, for example, such as 64a, 66a, and 68a, and are located opposite a source, such as 62a. Only a single detector 70 is shown located opposite source 62e, although a group of detectors could also be located opposite source 62e.

IR sources 62, collectively, are driven by signals generated in the processor/pump module 16 and transmitted to IR sources 62a through 62e via conductors 72a through 72e, respectively. Similarly, output signals from individual detectors 64a through 64e, 66a through 66e, 68a through 68e, and 70 are transmitted to processor/pump module 16 via conductors 74a through 74e, 76a through 76e, 78a through 78e, and 80, respectively. Conductors 72, collec-

- 22 -

tively, are dressed together to form a signal cable 82, while conductors 74 collectively, 76 collectively, 78 collectively, and 80 are dressed together to form a signal cable 84. Cables 82 and 84 are merged together into a single signal cable 86 (see Figure 6), which connects sensor assembly 58 to processor/pump module 16.

As with conductors 36, 38, and 40, conductors 72, 74, 76, 78, collectively, and 80 can be either electrical conductors or optical fibers. That is, the IR sources 62, collectively, and the IR detectors 64, 66, 68, collectively, and 70 may be located either within sensor assembly 58 itself, in which case the conductors are electrical conductors and carry electrical signals between processor/pump module 16 and sensor assembly 58, or within processor/pump module 16, in which case the conductors are optical fibers and carry infrared radiation between processor/pump module 16 and sensor assembly 58.

IR radiation generated by IR sources 62, collectively, is directed through peritoneal tissue 52, and thus the blood flowing through the tissue, to detectors 64, 66, 68, collectively, and 70 located across from the IR sources. As in the previous embodiment, each source or detector may have associated with it a narrow band filter, so that each optical source and the detectors associated with it in a given array operate in only a discrete narrow band of IR radiation. The IR radiation detected by detectors 64, 66, 68, collectively, and 70 is, of course, affected by its interaction with tissue 52 and the blood flowing therethrough. Consequently, by analyzing the output signals from the detectors, it is possible to derive information about the blood flowing through tissue 52. Preferably, although not necessarily, selected sensor/detector pairs are used for different measurement techniques, such as, for example, infrared transmittance, infrared reflectance, and infrared scattering. Thus, the output signals from the individual detectors can be processed differently to obtain different characteristics of the blood being measured.



*Alternative Sensor Configuration*

A third embodiment 88 of sensor assembly is illustrated in Figures 9 and 10. In those figures, sensor assembly 88 comprises a generally rectangular array of source/detectors 90 disposed on opposite halves 92 and 94 of the sensor assembly, with each half being on opposite sides of a vascular membrane 52. Source/detectors 90 are preferably, although not necessarily, arranged opposite one another on respective halves 92 and 94, so that the array on one half is substantially in alignment with the array on the other half.

An individual source/detector 90 is illustrated in more detail in Figure 11. Source/detector 90 is generally circular, and at its center portion contains a source segment 96, from which infrared radiation is emitted. An inactive buffer ring 98 surrounds source segment 96. A second inactive buffer ring 100 is radially spaced from and surrounds buffer ring 98. Buffer rings 98 and 100 are inactive in the sense that they neither emit nor respond to IR radiation. The portion of source/detector 90 between buffer rings 98 and 100 is divided into a plurality of detector segments 102, each of which is associated with a narrow band filter so that it responds to a selected band of radiation. A linearly-variable filter can be used, for example. In this manner, each detector segment 102 operates in only a discrete narrow band. A second plurality of detector segments 104 is located radially outward of buffer ring 100, each of which is also associated with a narrow band filter so that it, too, responds to a selected band of radiation.

It will be appreciated that a single source/detector 90 can operate to measure both reflected and scattered IR, or a single pair of source/detectors 90 can operate to measure reflected, scattered, and transmitted light over a plurality of discrete radiation bands.

Figure 12 illustrates an embodiment 106 of a sensor assembly similar to those shown in Figures 7 and 10, except that the two halves 108 and 110 are not spaced apart by a fixed distance, as are the halves of the detectors in Figures 7 and 10. Instead, the halves 108 and 110 are movable toward and away from each other, and the gap 112 may be adjusted by means of adjusting

screws 114. Preferably, the head portion of screw 114 is made captive, but freely rotatable, in one half, such as half 108. The shank portion of the screw is received in a threaded bore 116 in the opposite half. Thus, by rotating screw 114, the width of the gap 112 between halves 108 and 110 can be easily adjusted for optimum spacing of the individual sources and detectors relative to the vascular membrane 52.

### Oxygenation and Tissue Perfusion Monitoring

Figure 13b illustrates this concept can be summarized using the following equations:

A. Oxygen delivery = cardiac output X oxygen saturation (%) x hemoglobin concentration (gm/dl) X 1.39 + partial pressure of oxygen (PaO<sub>2</sub>) x 0.0031

B. Cardiac output = heart rate x stroke volume

Cardiac output is a measurement of blood flow (liters/minute) and can be defined as the heart rate times the stroke volume. The stroke volume is the amount of blood ejected with each beat of the heart and is influenced by the amount of blood returning to the heart, the state of contractility of the heart muscle, and degree of afterload or impedance to forward blood flow. (72 bts/min  $\times$  80 ml/bt = 5,760 ml/min). Heart rate can be measured by counting the plethysmograph pulse wave as shown in Figure 13b.

Stroke volume can be estimated by analyzing the plethysmograph pulse wave illustrated in Figure 13d including the maximum amplitude, the area under the curve, the rate of upstroke, and the velocity of wave propagation according to standard processing techniques. Current research is correlating pulse wave analysis with invasive monitoring such as Swan Ganz catheters and transesophageal echocardiography. Current pulse oximeter technology displays a pulse wave reflecting the volume of blood perfusing the tissue between the

- 25 -

source and detector. Pulse detection algorithms evaluate the changes in light attenuation across a vascular tissue (photoplethysmography). The optical path length of the diastolic tissue bed and the optical path length of the systolic tissue bed is measured. The difference between the two is the optical path length of light being affected only by arterial blood. The microprocessor continually calculates the ratio of light absorption associated with both wavelengths of light emitted by the two source diodes. With diminished blood flow, conventional pulse oximeters increase the gain on the signal with no attempt to measure blood flow or pulse wave velocity. With sufficient gain on the signal and noise rejection algorithms, an accurate oxygen saturation measurement can be maintained despite a fall in tissue blood flow to less than 10% of baseline. Some commercially available pulse oximeters display the signal gain required (2x, 4x, 8x, etc.) to maintain a normal amplitude plethysmograph waveform and an accurate hemoglobin oxygen saturation reading. Analysis of the raw signal that produces the pulse wave includes the maximum amplitude, the area under the curve, the rate of upstroke, and the velocity of wave propagation. This raw signal data can be used to estimate the stroke volume per beat of the heart (volume of blood ejected per beat). The velocity of wave propagation can be measured using two or more source/detector pairs in series such that the pulse wave is detected with a slight time delay at the second pair and an additional time delay at the third. Since the distance between the sensor pairs is known and fixed, a pulse wave velocity can be calculated. The total combined analysis of the pulse wave will be used to estimate stroke volume and therefore an on-line estimate of cardiac output.

The amount of radiation absorption and scattered is significantly diminished by using a thin translucent vascular membrane as the optical interface. A higher signal to noise ratio is found compared to non-invasive pulse oximetry techniques.

C. Oxygen content within the blood = hemoglobin oxygen saturation (%) x hemoglobin concentration (gm/dl) X 1.39 + partial pressure of oxygen (PaO<sub>2</sub>) x 0.0031

- 26 -

Hemoglobin oxygen saturation reflects the sigmoidal shaped dissociation curve in which hemoglobin is 98% saturated or greater when the partial pressure of oxygen exceeds 100 mm Hg. Saturation slowly falls such that hemoglobin is 95% saturated at an oxygen partial pressure of 60 mm Hg.  
5 Below this partial pressure, oxygen saturation falls dramatically. Commercially available pulse oximeter technology provides this information accurately and reliably.

Infrared spectroscopy is able to accurately measure blood hemoglobin concentration. Since 1.39 milliliters of oxygen can bind to each  
10 gram of hemoglobin, the total oxygen content of the blood can therefore be measured using optical means. The amount of oxygen dissolved in the plasma is negligible (partial pressure of oxygen (PaO<sub>2</sub>) x 0.0031) and of little clinical significance.

The purpose of the implantable oxygenation, hemoglobin, and  
15 perfusion sensor is to obtain frequent objective data on patients with chronic illnesses such as heart failure and respiratory failure. Patients would be monitored for changes in hemoglobin oxygen saturation (pulse oximeter), hemoglobin concentration (infrared measurement), and changes in tissue perfusion (analysis of the photoplethsmograph waveform) for the purpose of  
20 detecting cardiovascular decompensation early so that the physician can manage the problem as an outpatient. Visits to the emergency room and admissions to the ICU would significantly diminish. Data from the sensors will be stored within a memory chip and reviewed by the physician during an office visit or over the phone. In one embodiment, the physician would be notified  
25 automatically if data changed significantly from the individual patient's normal pattern. Typically, patients wait until significant cardiovascular decompensation has produced overt symptoms requiring admission through the emergency room to the ICU. With this implantable sensor, physicians will be able to detect early decompensation and institute corrective therapy as an outpatient. Data stored  
30 in the memory chip will provide the clinician with the natural history of the disease process. The physician will be able to titrate medical therapy based on

- 27 -

objective numbers and conclude from the data the benefits incurred by this therapy. All of the major determinants of oxygen delivery to the tissues can be measured with this sensor. For example, a patient develops heart failure and pulmonary edema following a myocardial infarction. Once stabilized in the ICU  
5 a sensor would be implanted under local anesthesia and data collected on-line. Once discharged from the hospital, the sensor would monitor the patient for significant changes in oxygenation, perfusion, hemoglobin concentration, and cardiac arrhythmia. If no significant changes occur, data would be stored in a memory chip and downloaded for physician interpretation during the patient's  
10 routine office visit. Medications that improve cardiac contractility and improve tissue blood flow could be titrated to objective endpoints rather than to vague patient symptoms.

Alternate clinical uses for this optical technology include integration of the output signal with an internal cardiac defibrillator (ICD).  
15 Patients are implanted the ICD following a near death experience due to a serious ventricular arrhythmia of the heart. Unfortunately, the electrocardiogram algorithms programmed into the ICD are unable to differentiate a life threatening arrhythmia from noise in certain cases. It is estimated that inappropriate defibrillation occurs 30% of the time. Using the  
20 implantable photoplethsmograph sensor (pulse oximeter), tissue blood flow data can be integrated with the algorithm for defibrillation. Both the ECG and tissue blood flow have to agree that a life threatening arrhythmia is present before defibrillation.

Closed-loop feedback with a programmable pacemaker provides  
25 a means to increase/decrease the heart rate and fine tune the timing intervals of a pacemaker to more physiologically meet the oxygenation and perfusion needs of the tissues during various levels of physical activity. The sensor would be placed on around a central vein returning to the right heart.

Measurement of venous oxygen saturation reflects the adequacy  
30 of cardiac output and oxygen delivery to the peripheral tissues. During exercise, blood flow increases several fold to the muscles and other tissues.

- 28 -

When the heart is paced at a fixed low rate, the tissues extract a greater percentage of the oxygen delivered. Low venous saturation suggests the need to increase oxygen delivery by increasing the cardiac output and by increasing the oxygen carrying capacity of the blood ( transfusion red blood cells, iron therapy ). Decreasing venous oxygen saturation would signal the pacemaker to increase the heart rate and to optimize the timing intervals between atrial and ventricular contraction thus regulating the cardiac output of the heart. Once the oxygen debt was satisfied, the heart rate would slowly return to baseline values. In this way, the pacemaker would compensate for an increased demand for oxygen in the peripheral tissues.

Figure 13a illustrates a functional block diagram of a blood oxygen and perfusion monitoring and control system 200 comprising an implanted sensor 330 (shown in Figure 13c) and an implanted control module 300 (not shown in detail) which is in communication with an extracorporeal monitor 210. The extracorporeal monitor 210 is in communication with a direct blood calibration module 400 (explained in detail below) and other communication systems such as, but not limited to, a cellular telephone 220, an emergency medical warning system (not shown), or a hand held monitoring device (shown in Figure 18b).

The blood oxygen perfusion monitoring and control module 200 is surgically implanted in a patient where it is employed to measure, control, monitor, and report measured hemoglobin oxygen saturation and tissue perfusion. As shown in Figure 13b, measured blood oxygen is represented as the amount of oxygen delivered to the blood on a pulse by pulse basis as the blood is pumped by the heart. The amount of blood oxygen delivered to the body can be represented according the following formula:

$$O_2 \text{ (Delivered)} = C.O. * Hb * SaO_2 * 1.39 + PaO_2 * 0.0031,$$

where,

C.O. = Cardiac Output = Heart rate x stroke volume  
liters/mn,

Hb = Hemoglobin concentration mg/dl,

- 29 -

$SaO_2$  = Hemoglobin oxygen saturation %,

1.39 = a constant representing 1.39 ml of oxygen bound  
to one gram of Hemoglobin,

$PaO_2$  = partial pressure of oxygen dissolved in plasma.

5 and

0.0031 = a constant representing the amount of oxygen  
dissolved in plasma.

The blood oxygen is measured as an estimate of oxygen according  
to the pulsatile perfusion of the blood through a vascular interface. It is to be  
10 understood that the vascular interface can be, but is not limited to, an artery,  
a vein, a vascular membrane, or vascular tissue. The oxygen measurement is  
acquired according to standard pulse oximetry described above. In a preferred  
embodiment of the present invention, oxygen is measured by the implanted  
control module 300 and at least one paired sensor assembly 330 (shown in  
15 Figure 13c).

Figure 13c illustrates an embodiment of the sensor assembly 330  
assembly similar to those shown in Figures 7, 10 and 12. However, the two  
halves 310 and 320 have linearly arrayed elements that are spaced apart by a  
distance defined by a vascular membrane 340. The linear arrays are paired  
20 together to form a plurality of paired arrays as may be required to acquire a  
plethysmographic representation of the pulsatile flow of oxygenated and reduced  
hemoglobin passing through the vascular membrane 340. A single paired array  
is required to produce a plethysmograph as shown in Figure 13b, and, multiple  
arrays, are required to measure a velocity of the pulse wave.

25 In the embodiment of sensor 330 illustrated in Figures 13c, the  
optical sources and optical detectors may be infrared (IR) sources and IR detec-  
tors, although radiation from infrared through the visible spectrum may be  
employed without departing from the invention. In the figures, individual IR  
sources 310 a-d and individual IR detectors 320 a-d are grouped together in  
30 pairs forming the paired array 330. A plurality of paired arrays will also com-  
prise an plurality of IR sources and IR detectors respectively. The individual

- 30 -

IR sources 310 a-d may be miniature infrared diodes located, in the illustrated embodiment, on one side of the vascular membrane 340. IR sources 310 a-d are driven by signals generated in the control module 300 and transmitted to the IR sources 310 a-d via conductors (not shown). Similarly, output signals from individual detectors 320 a-d are transmitted to the control module 300 via separate conductors (not shown).

Each IR source 310 and detector 320 may have associated with it an optical filter (not shown) or a time based or encoded discriminator (not shown) for selectively emitting and detecting the selected bands of radiation emitted for detecting blood oxygen saturation.

With this embodiment, the IR sources 310 and detectors 320 are arranged diametrically opposite each other to detect light transmitted through the vascular membrane 340.

It is important to note that, although this embodiment of the invention is described using a single array of paired IR sources and associated detectors, that precise configuration is not crucial to the invention. In fact, the invention may be implemented, for example, using a plurality of paired arrays for detecting reflected, scattered, and transmitted IR radiation.

Figure 13d shows a plethysmographic representation of pulsatile blood oxygen perfusion when four paired arrays are employed.

The implanted control module 300 preferably incorporates a pulse oximeter module (not shown) for producing perfusion data (as shown in Figure 13d). Also incorporated in the control module 300 is a processor module (not shown) for analyzing the perfusion data and for producing a control signal that is communicated by the control module 300 to a blood oxygen regulating device such as, but not limited to, a pacemaker or defibrillator.

Figure 14 is an illustration of a preferred aspect of the invention showing a control module 300 having a sensor 330 for measuring perfusion data to determine the level of blood oxygen. The sensor 330 as explained above employs at least two selected bands of frequencies to produce detected signals



- 31 -

corresponding to oxygenated hemoglobin levels which are analyzed by the processor module (not shown) of the control module 300.

The control module 300 also incorporates a communication module (not shown) for communicating control information to an implanted  
5 pacemaker 360. The pacemaker 360, in response to the control information received from the control module 300, regulates the heart 1000 (shown for illustrative purposes) to pump blood as required to produce a desired blood oxygen level. The control module 300 controls blood oxygen by regulating the  
10 pacemaker to control heart rate and timing of atrial and ventricular contraction according to stored blood oxygen values programmed into the control module 300. Programmed blood oxygen values are stored in the control module 300 through its communication module. An extracorporeal communication device (shown in Figure 18a) is used to control and calibrate the control module 300 which is explained in detail below.

15 Figure 15a is an illustration of another preferred aspect of the invention showing a control module 300 having a sensor 330 for measuring perfusion data to estimate quantity of blood delivered per beat to the tissues. The control module 300 incorporates a communication module (not shown) for communicating control information to an implanted defibrillator 380. The  
20 defibrillator 380, in response to the control information from the control module 300 and its own internal EKG system 381 (shown for illustrative purposes) will regulate the heart 1000 (shown for illustrative purposes) to prevent inappropriate in other words the discharge of the internal defibrillator.

It is known that an internal defibrillator will at times  
25 inappropriately defibrillate irregular heart beat patterns. When this occurs the level of blood oxygen can be severally affected. To prevent this condition, the level of blood oxygen measured by the control module 300 is used to confirm proper heart function. Because the control module 300 and sensor 330 use photo-plethysmography to measure pulsatile perfusion, actual defibrillation can  
30 be detected as an instantaneous loss of blood oxygen.

- 32 -

In Figure 15a the electrical activity of the heart normal sinus rhythm with satisfactory tissue perfusion and oxygenation noted on the plethysmography waveform. As the trace pressures the cardiac rhythm degenerates into ventricular tachycardia and then ventricular fibrillation. The tissue perfusion and oxygenation also deteriorates such that pulsatile flow is lost.

Figure 15b represents a continuation of the ventricular fibrillation trace and lack of pulsatile tissue bound flow at timex. The internal defibrillation produces an electrical shock that converts the cardiac rhythm to normal with satisfactory pulsatile tissue blood flow.

Figure 15a illustrates vascular tissue plethysmography with a simultaneous and EKG recording of the heart. Therefore, the use of perfusion data to control blood oxygen by preventing cardiac defibrillation is a very important feature of the invention. This feature provides increased assurance that blood oxygen will be maintained consistently without disruptions caused by inappropriate heart fibrillation.

#### *Specific Blood Constituent Monitoring, Control and Reporting System*

Naturally, it should be understood that, although embodiments using different groupings of sources and detectors have been described for the measurement and control of blood glucose and blood oxygen, the invention is not in any way limited to either a specific number of source/detector groupings or blood constituents, nor is it absolutely necessary that the sources and detectors be arranged in specific configurations.

Figures 16a is a schematic representation of an infrared sensor 330 and its control module 300 equipped with a communication module (not shown) according to a another preferred embodiment of the present invention. The control module 300 and sensor 330 are implanted into the body subcutaneously just below the skin. The sensor 330 is placed about a vein, an artery or inserted into vascular tissue allowing it to measure and control selected blood constituents. The control module 300 through its communication module can communicate the measured level of blood constituent extracorporeally by

- 33 -

means of its communication module to devices such as, but not limited to, an external monitoring and warning device, or a telecommunication network.

Figure 16b is a schematic representation of the infrared sensor 330 shown in Figure 16a used to measure and control a medicinal blood constituent such as an antibiotic which is used to treat a localized infection 392 (shown for illustrative purposes). It is to be understood that this invention is not limited to this embodiment, but may be used to deliver, measure and control any medicinal blood constituent such as, but not limited to, chemotherapy and cardiac medications. In addition, the measured level of medication in the blood can be monitored extracorporeally by a monitoring device or provide to a remote location by means of an external communication system adapted to a telecommunication network.

In addition, to controlling blood constituents, the sensor 330 and control device 300 can be used to measure and report blood constituent levels extracorporeally to remote monitoring equipment. For example, blood constituents such as tumor markers including, but not limited to, prostate specific antigen (PSA) for detecting prostate cancer and colon embryonic antigen (CEA) for detecting colon cancer, can be continuously monitored safely and conveniently without the need and inconvenience of constantly drawing blood and laboratory testing. By measuring these tumor markers on a daily basis, recurrence of tumor will be detected early prior to spread throughout the body. This can be accomplished by selecting the appropriate optical sensors and detector and operating bandwidths for interaction with each specific blood constituent.

For example and as explained above, blood oxygen can be measured through oxygenated hemoglobin with two pairs of sensors and detectors operating at 660 nanometers and 940 nanometers for detecting oxygenated and reduced hemoglobin.

*Implantable Optic Sensor Interface (IOSI)*

- 34 -

Figure 17a is a schematic representation of an infrared sensor 1330 according to another preferred embodiment of the present invention. The sensor 1330 is shaped like a tuning fork and is implanted surgically into vascular tissue. The shape facilitates insertion and retention into vascular rich  
5 tissue such as a muscle or vascular membrane as shown in Figures 17b and 17c. The sensor has two parallel arms 1320 joined at one end and separated from each other by a fixed distance. Each arm has a pointed tip 1332 at its other end for piercing the tissue. As the sensor is inserted into the tissue a vascular interface 1334 is formed between the arms 1310, 1320. The arms 1310, 1320  
10 have at least one electromagnetically sensitive array comprising optical sources and detectors for illuminating the vascular interface 1340 and detecting a desired blood constituent described above.

Figure 18a is an illustration of an extracorporeal calibration and communication module 410. Figure 18b is an illustration of a hand held  
15 monitor, display and communication unit 450 for use in connection with implantable blood constituent sensors and control modules described above. The calibration and control module 410 communicates with a communication module (not shown) associated with the implanted control module 300, providing calibration data and extracorporeal display and reporting of the  
20 measured data produced by the control module 300.

The extracorporeal calibration and communication module 410 communicates calibration data directly to the implanted control module 300 allowing precise calibration of the measurements made by the control module 300 and its sensor 330. Calibration data is produced by the extracorporeal  
25 calibration and communication module 410 by commercially available methods such as glucose oxidase reagent strips 420.

The communication module 410 and the control module 300 are equipped with commercially available communication means adapted for inter-corporeal communication.

- 35 -

Figure 18c is a functional block diagram showing the operation of an implantable device according to the invention in communication with the extracorporeal calibration and communication module shown in Figure 18a.

#### *Extracorporeal Calibration and Communication Modules*

5 As already noted, processor/pump module 16 contains an electronic microprocessor and associated electronic circuitry for generating signals to and processing signals from sensor assembly 14 and for generating control signals to the insulin pump itself. The microprocessor is preferably programmed to execute algorithms to perform multispectral correlation, and matched  
10 digital bandpass filtering to remove low frequency bias and high frequency noise. Such algorithms are well-known to those skilled in the art, and need not be described in detail. Moreover, the invention is not limited to any specific algorithm; rather, any algorithms suitable for performing the desired multispectral correlation and filtering functions may be used without departing  
15 from the invention. It should also be noted that, while the present invention provides accurate glucose level measurements, accurate measurement is not crucial to the control of the insulin pump 16. In a manner similar to the way a house thermostat operates, the pump 16 can be controlled to release a fixed quantity of insulin until the glucose levels falls below a preselected level. Thus,  
20 any algorithm capable of such control is within the scope of the invention. The algorithm may also control insulin pump 16 to release a glucagon bolus, (1 mg of glucagon, when blood glucose levels trend below 60 mg/dl will increase the blood glucose level above 150 mg/dl).

Processor/pump module 16 may also contain a telemetry transmit-  
25 ter to transmit sensor data to an external processor and external insulin pump. Insulin can be injected subcutaneously or into a subcutaneous infusaport for delivery into the peritoneal cavity or into a portal vein.

Processor/pump module 16 may also consist of a telemetry receiver for external calibration. If recalibration is necessary, the system  
30 may be recalibrated externally by comparison to a weekly or monthly finger

- 36 -

stick blood glucose measurement, such as, for example, using calorimetric assay of a glucose oxidase/hydrogen peroxide reaction using standard techniques. The absolute glucose amount from the external calibration measurement can then be telemetered to the processor for calibration.

5                   Alternatively, each source of radiation may consist of multiple discrete bands of light with a unique temporal or frequency modulation, allowing discrimination of the different spectral bands.

                  Alternatively to providing a narrow band filter for each detector, the different spectral bands from the sources are each modulated in a unique  
10                   temporal or frequency fashion, allowing for discrimination of the different spectral regions and obviating the need for narrow band filters.

                  In another embodiment, source 310 a (or 310 b, 310 c, or 310 d) may consist of multiple LEDs or multiple laser diodes, each of a different wavelength spaced identically collinear or spaced very closely so that each  
15                   wavelength has substantially the identical optical path and interacts with substantially identical tissue. The detector 320 a, b, c, or d detects light from each individual wavelength from source 320 a, b, c, or d, respectively.

                  The processor discriminates amongst the different wavelengths by having each wavelength pulse at a different frequency or at a different time. As  
20                   the processor can discriminate amongst the different wavelengths by either different frequency or temporal information, narrow wavelength filters 46 a, 48 a, and 50 a are unnecessary in this embodiment. Multiple sources and multiple detectors provide redundancy or alternatively the ability to measure different chemical species, although in many cases a single source and detector is  
25                   adequate. The operation of the sensor is otherwise the same as described in the previous embodiment.

#### *Fourier Transform Infrared Spectroscopy (FTIR) Analysis*

                  Using commercially available Fourier transform infrared spectroscopy (FTIR) analysis, it is possible to correlate the sensor output data  
30                   with blood glucose levels, blood fatty acid levels, and blood amino acid levels.

- 37 -

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

- 38 -

### CLAIMS

1. An implantable device for sensing In-vivo the level of at least one blood constituent in mammalian vascular tissue, comprising  
at least one source of radiation from infrared through visible light, arranged to direct said radiation at said tissue, said radiation being affected by interaction with said tissue, and  
a plurality of detectors, each having associated with it a filter transparent to a discrete narrow band of radiation, each detector providing an output signal representative of detected radiation in said narrow band, the detectors being located with respect to the tissue to receive radiation affected by said tissue.
2. The implantable device according to claim 1, further comprising a channel having an internal circumference around which are arranged said source and said detectors, said channel being dimensioned to receive a blood vessel therein and locate said vessel in proximity to said source and detectors.
3. The implantable device according to claim 1, further comprising a first half and a second half, one half supporting said at least one source and the other half supporting at least one of said plurality of detectors, said halves being spaced apart and defining a gap therebetween for receiving said vascular tissue therein and locating said tissue in proximity to said source and detectors.
4. The implantable device according to claim 3, further comprising said halves being separate from one another and movable reciprocally toward and away from each other for varying the size of said gap.
5. The implantable device according to claim 4, further comprising an adjustable fastener for adjustably fastening said halves together for adjustably varying the size of said gap.
6. The implantable device according to claim 5, wherein the adjustable fastener comprises a rotatable screw in one of said halves and a threaded bore receiving said screw in the other of said halves.



- 39 -

7. The implantable device according to claim 1, wherein said at least one source and said plurality of detectors are arranged in a linear array, at least one of said plurality of detectors being located opposite said source and spaced therefrom by a distance sufficient to receive said tissue between said source and said detector.

8. The implantable device according to claim 1, wherein said at least one source and said plurality of detectors are arranged in a planar array, at least one of said plurality of detectors being located opposite said source and spaced therefrom by a distance sufficient to receive said tissue between said source and said detector.

9. The implantable device according to claim 1, wherein at least one of said detectors is located opposite said source and at least one of said detectors is located next to said source.

10. The implantable device according to claim 1, wherein at least one of said plurality of detectors is located to detect radiation scattered by said tissue.

11. The implantable device according to claim 1, wherein at least one of said plurality of detectors is located to detect radiation transmitted through said tissue.

12. The implantable device according to claim 1, wherein at least one of said plurality of detectors is located to detect radiation reflected by said tissue.

13. The implantable device according to claim 1, wherein at least one of said plurality of detectors is located to detect radiation scattered by said tissue and at least one of said plurality of detectors is located to detect radiation transmitted through said tissue.

14. The implantable device according to claim 1, wherein at least one of said plurality of detectors is located to detect radiation scattered by said tissue, at least one of said plurality of detectors is located to detect radiation transmitted by said tissue, and at least one of said plurality of detectors is arranged to detect radiation reflected by said tissue.

- 40 -

15. The implantable device according to claim 1, wherein at least one optical fiber is used in conjunction with at least a selected one of said source and detectors for conveying said radiation between said selected one of said source and detector and said tissue.

16. The implantable device according to claim 1, further comprising a communication means responsive to said processor module for communicating said control signal representative of the level of said blood constituent to a receiving device.

17. The implantable device according to claim 16, wherein said blood constituent is selected from a group consisting of glucose, oxygen, hemoglobin medicinal therapies, and tumor markers.

18. A device for measuring and controlling the level of blood glucose in a mammal, comprising

an implantable infrared source and sensor module for directing infrared radiation through vascular tissue and for sensing the infrared radiation after it has passed through the tissue and generating an output signal representative of the sensed infrared radiation,

a processor module responsive to the output signal from the infrared source and sensor module for performing spectral analysis of the output signal and deriving therefrom a control signal representative of the level of said blood glucose, and

an insulin pump for dispensing doses of insulin in response to the control signal.

19. The device for measuring and controlling the level of blood glucose in a mammal according to claim 18, wherein the insulin pump is external to the body of the mammal.

20. The device for measuring and controlling the level of blood glucose in a mammal according to claim 18, wherein the insulin pump is implantable within the body of the mammal.

21. The device for measuring and controlling the level of blood glucose in a mammal according to claim 18, wherein the source and

- 41 -

sensor module comprises at least one source of radiation from infrared through visible light, arranged to direct said radiation at said tissue, said radiation being affected by interaction with said tissue, and a plurality of detectors, each having associated with it a filter transparent to a discrete narrow band of radiation, each detector providing an output signal representative of detected radiation in said narrow band, the detectors being located with respect to the tissue to receive radiation from said source affected by said tissue.

22. The device for measuring and controlling the level of blood glucose in a mammal according to claim 18, wherein the source and sensor module comprises at least one source of radiation for emitting at least one selected band of radiation from infrared through visible light at said blood in said tissue, said radiation being affected by interaction with said tissue, and at least one detector adapted to receive said at least one selected band of affected radiation, each detector providing an output signal representative of said affected radiation.

23. The device for measuring and controlling the level of blood glucose in a mammal according to claim 18, further comprising a communication means responsive to said processor module for communicating said control signal representative of the level of said blood glucose to a receiving device.

24. The device for measuring and controlling the level of blood glucose in a mammal according to claim 23, further comprising a calibration system responsive to said communication means and said processor module for receiving calibration signals from another device for calibrating said signal representative of the level of said blood glucose.

25. A combined optical source and detector comprising  
a substrate,  
a source of optical radiation located on a portion of said substrate, and

- 42 -

a plurality of optical detector elements located on said substrate adjacent said source for receiving optical radiation emitted by said source and affected by interaction with a target.

26. A combined optical source and detector as in claim 25, wherein each detector element has associated with it a filter transparent to a discrete narrow band of radiation, each detector element providing an output signal representative of detected radiation in said narrow band.

27. A device for sensing In-vivo the level of at least one constituent of blood within mammalian vascular tissue, comprising

at least one implantable source of radiation from infrared through visible light, arranged to direct said radiation at blood within said tissue and being located out of direct contact with said blood, said radiation being affected by interaction with said blood,

at least one implantable detector located out of direct contact with said blood and being located with respect to the tissue to receive radiation affected by interaction with said blood,

means associated with said source and said detector for deriving from said detector at least one output signal containing information within selected bands of frequencies from infrared through visible light, and

a processor for processing said signal to derive information about the level of said blood constituent.

28. The device according to claim 27, wherein said means associated with said source and said detector comprises a filter transparent to at least two discrete narrow bands of radiation.

29. The device according to claim 27, further comprising a channel having an internal circumference around which are arranged said source and said detector, said channel being dimensioned to receive a blood vessel therein and to locate said vessel in proximity to said source and detectors.

30. The device according to claim 27, further comprising a first half and a second half, one half supporting said at least one source and the other half supporting said at least one detector, said halves being spaced apart

- 43 -

and defining a gap therebetween for receiving said vascular tissue therein and locating said tissue in proximity to said source and detectors.

31. The device according to claim 29, further comprising said halves being separate from one another and movable reciprocally toward and away from each other for varying the size of said gap.

32. The device according to claim 31, further comprising an adjustable fastener for adjustably fastening said halves together for adjustably varying the size of said gap.

33. The device according to claim 32, wherein the adjustable fastener comprises a rotatable screw in one of said halves and a threaded bore receiving said screw in the other of said halves.

34. The device according to claim 27, wherein said at least one detector is located opposite said source and spaced therefrom by a distance sufficient to receive said tissue between said source and said detector.

35. The device according to claim 27, further comprising a plurality of detectors wherein at least one of said detectors is located opposite said source and at least one of said detectors is located next to said source.

36. The device according to claim 35, wherein at least one of said plurality of detectors is located to detect radiation scattered by said blood.

37. The device according to claim 35, wherein at least one of said plurality of detectors is located to detect radiation transmitted through said blood.

38. The device according to claim 35, wherein at least one of said plurality of detectors is located to detect radiation reflected by said blood.

39. The device according to claim 35, wherein at least one of said plurality of detectors is located to detect radiation scattered by said blood and at least one of said plurality of detectors is located to detect radiation transmitted through said blood.

40. The device according to claim 35, wherein at least one of said plurality of detectors is located to detect radiation scattered by said blood, at least one of said plurality of detectors is located to detect radiation transmit-

- 44 -

ted by said blood, and at least one of said plurality of detectors is arranged to detect radiation reflected by said blood.

41. The device according to claim 27, wherein at least one optical fiber is used in conjunction with at least a selected one of said source and detector for conveying said radiation between said selected one of said source and detector and said tissue.

42. The device according to claim 27, further comprising a telemetry transmitter for transmitting said information about the level of said blood constituent to an external device.

43. The device according to claim 27, further comprising a telemetry receiver for receiving signals from an external device.

44. The device according to claim 43, wherein said signals from an external device are calibration signals.

45. The device according to claim 27, further comprising a telemetry transmitter for transmitting said information about the level of said blood constituent to an external device and a telemetry receiver for receiving signals from said external device.

46. A device for measuring and controlling the level of blood glucose in a mammal, comprising

an implantable infrared source and sensor module for directing infrared radiation through vascular tissue and for sensing the infrared radiation after it has passed through the tissue and through blood in said tissue and generating an output signal representative of the sensed infrared radiation,

a processor module responsive to the output signal from the infrared source and sensor module for performing spectral analysis of the output signal and deriving therefrom a control signal representative of the level of said blood glucose, and

an insulin pump for dispensing doses of insulin in response to the control signal.

47. The device according to claim 46, wherein the insulin pump is external to the body of the mammal.

- 45 -

48. The device according to claim 46, wherein the insulin pump is implantable within the body of the mammal.

49. The device according to claim 46, wherein the source and sensor module comprises at least one implantable source of radiation from infrared through visible light, arranged to direct said radiation at blood within said tissue and being located out of direct contact with said blood, said radiation being affected by interaction with said blood, at least one implantable detector located out of direct contact with said blood and being located with respect to the tissue to receive radiation affected by interaction with said blood, means associated with said source and said detector for deriving from said detector at least one output signal containing information within selected bands of frequencies from infrared through visible light, and a processor for processing said signal to derive information about the level of said blood glucose.

50. A method of performing In-vivo optical spectroscopy analysis of blood in a mammal, comprising the steps of

implanting in vascular tissue and out of direct contact with blood to be analyzed a source of radiation having wavelengths within a preselected range of wavelengths and positioning said source to direct said radiation at said blood, said radiation being affected by interaction with said blood,

implanting a detector responsive to said radiation out of direct contact with said blood and positioning said detector to receive radiation affected by said blood,

obtaining from said detector an information-containing output signal, and

analyzing the information contained in said output signal and deriving therefrom information about levels of at least one blood constituent within said blood.

51. The method according to claim 50, wherein the step of analyzing the information contained in said output signal includes Fourier transform infrared spectroscopy.

- 46 -

52. The method according to claim 51, further comprising performing said Fourier transform infrared spectroscopy on portions of said radiation affected by said blood within two separate narrow bands of wavelengths within said preselected range.

53. The method according to claim 50, further comprising the step of limiting radiation directed at said blood to two separate narrow bands of wavelengths within said preselected range.

54. The method according to claim 53, wherein said step of limiting radiation directed at said blood comprises optically filtering said radiation.

55. The method according to claim 50, further comprising the step of limiting radiation received by said detector to two separate narrow bands of wavelengths within said preselected range.

56. The method according to claim 55, wherein said step of limiting radiation received by said detector comprises optically filtering said radiation.

57. A device for measuring and controlling the level of blood oxygen in a mammal, comprising

an implantable infrared source and sensor module for directing infrared radiation through vascular tissue and for sensing the infrared radiation after it has passed through the tissue and generating an output signal representative of the sensed infrared radiation,

a processor module responsive to the output signal from the infrared source and sensor module for performing spectral analysis of the output signal and deriving therefrom a control signal representative of the level of said blood oxygen, and

a control device for controlling the level said blood oxygen in response to said control signal.

58. The device for measuring and controlling the level of blood oxygen in a mammal according to claim 57, wherein the control device is a pacemaker.



- 47 -

59. The device for measuring and controlling the level of blood oxygen in a mammal according to claim 57, wherein the second device is a defibrillator.

60. The device for measuring and controlling the level of blood oxygen in a mammal according to claim 57, wherein the source and sensor module comprises at least one source of radiation from infrared through visible light, arranged to direct said radiation at said tissue, said radiation being affected by interaction with said tissue, and a plurality of detectors, each having associated with it a filter transparent to a discrete narrow band of radiation, each detector providing an output signal representative of detected radiation in said narrow band, the detectors being located with respect to the tissue to receive radiation from said source affected by said tissue.

61. The device for measuring and controlling the level of blood oxygen in a mammal according to claim 57, wherein the source and sensor module comprises at least one source of radiation for emitting at least one selected band of radiation from infrared through visible light at said blood in said tissue, said radiation being affected by interaction with said tissue, and at least one detector adapted to receive said at least one selected band of affected radiation, each detector providing an output signal representative of said affected radiation.

62. The device for measuring and controlling the level of blood oxygen in a mammal according to claim 57, further comprising a communication means responsive to said processor module for communicating said control signal representative of the level of said blood oxygen to a receiving device.

63. The device for measuring and controlling the level of blood oxygen in a mammal according to claim 62, wherein said receiving device is an extracorporeal calibration module responsive to said control signal received from said communication means for communicating calibration signals to said processor module for calibrating said signal representative of the level of said blood oxygen.

- 48 -

64. The device for measuring and controlling the level of blood oxygen in a mammal according to claim 57, wherein the implanted source, sensor, and processor module comprises a pulse oximeter.

65. A device for measuring and controlling the level of medicinal blood constituent in a mammal, comprising

an implantable infrared source and sensor module for directing infrared radiation through vascular tissue and for sensing the infrared radiation after it has passed through the tissue and generating an output signal representative of the sensed infrared radiation,

a processor module responsive to the output signal from the infrared source and sensor module for performing spectral analysis of the output signal and deriving therefrom a control signal representative of the level of said medicinal blood constituent, and

a control device for controlling said medicinal blood constituent in response to said control signal.

66. The device according to claim 66, wherein said control device is a pump for dispensing doses of said medicinal blood constituent in response to the control signal.

67. The device according to claim 67, wherein the pump is external to the body of the mammal.

68. The device according to claim 68, wherein the pump is implantable within the body of the mammal.

69. The device according to claim 66, wherein the source and sensor module comprises at least one source of radiation from infrared through visible light arranged to direct said radiation at said tissue, said radiation being affected by interaction with said tissue, and a plurality of detectors, each having associated with it a filter transparent to a discrete narrow band of radiation, each detector providing an output signal representative of detected radiation in said narrow band, the detectors being located with respect to the tissue to receive radiation from said source affected by said tissue.

- 49 -

70. The device according to claim 66, wherein the source and sensor module comprises at least one source of radiation for emitting at least one selected band of radiation from infrared through visible light at said blood in said tissue, said radiation being affected by interaction with said tissue, and at least one detector adapted to receive said at least one selected band of affected radiation, each detector providing an output signal representative of said affected radiation.

71. The device according to claim 66, further comprising a communication means responsive to said processor module for communicating said control signal representative of the level of said medicinal blood constituent to receiving device.

72. The device according to claim 72, wherein said receiving device is an extracorporeal calibration module responsive to said control signal from said communication means for communicating calibration signals for calibrating said signal representative of the level of said medicinal blood constituent.

73. A device for sensing In-vivo the level of at least one constituent of blood within mammalian vascular tissue, comprising:

an implantable source of radiation emitting radiation in at least two selected bands between infrared and visible light, said source arranged to direct emitted radiation at blood within said tissue and being located out of direct contact with said blood, said emitted radiation being affected by interaction with said blood,

an implantable detector located out of direct contact with said blood and being located with respect to said tissue to receive radiation affected by interaction with said blood and generate an output signal in response to said affected radiation,

a communication means responsive to said detector output signal for communicating information in said output signal associated with said affected radiation, and

a processor in communication with said communication means for processing information communicated to the processor by said communication means to derive therefrom information about the level of said blood constituent.

74. The implantable device according to claim 74, further comprising a channel having a circular circumference around which is arranged said source and detector, said channel being dimensioned to receive a blood vessel therein and located such that said vessel is in proximity to said source and detectors, and the means for discriminating said signal by use of different spectral bands.

75. The implantable device according to claim 74, wherein said vascular tissue is a membrane and said emitted radiation from said source interacts with said membrane, said radiation being gathered by said detector.

76. The implantable device according to claim 74, wherein vascular tissue is a muscle and said emitted radiation from said source interacts with said muscle, said radiation being gathered by the detector.

77. The implantable device according to claim 74, wherein said bands of radiation comprise a spectra and means to discriminate said spectra, said means to discriminate spectra comprising modulation of said radiation as a selected function of time, and said processor having knowledge of said modulation.

78. The implantable device according to claim 74, wherein said bands of radiation comprise a spectra and means to discriminate said spectra, said means to discriminate spectra comprising modulation of said radiation at selected frequencies, and said processor having knowledge of said modulation.

79. The implantable device according to claim 74, which measures degrees of oxygen saturation in hemoglobin.

80. An implantable device according to claim 74, wherein said source comprises at least one LED of selected wavelengths.

81. The device according to claim 79, wherein said output signal is communicated to a pacemaker to regulate heart rate and time of atrial

and ventricular contractions in accordance with a predetermined level blood oxygen saturation.

82. A device according to claim 79, wherein said output signal is communicated to an implantable defibrillator to include tissue perfusion and oxygenation in the algorithm prior to defibrillation.

83. The implantable device according to claim 74, wherein said processor is located extracorporeally.

84. The implantable device according to claim 74, wherein said output signal is periodically calibrated according to a extracorporeal data acquired by measurement of a blood constituent by other known technique.

85. The implantable device according to claim 74 wherein said radiation source consists of at least two laser diodes.

86. The implantable sensor according to claim 84, wherein said blood constituent is at least blood glucose.

87. The implantable sensor according to claim 84, further comprising an audible alarm when a blood glucose level is determined by said processor to be in the hypoglycemic range.

88. The device according to claim 88, further comprising an insulin pump.

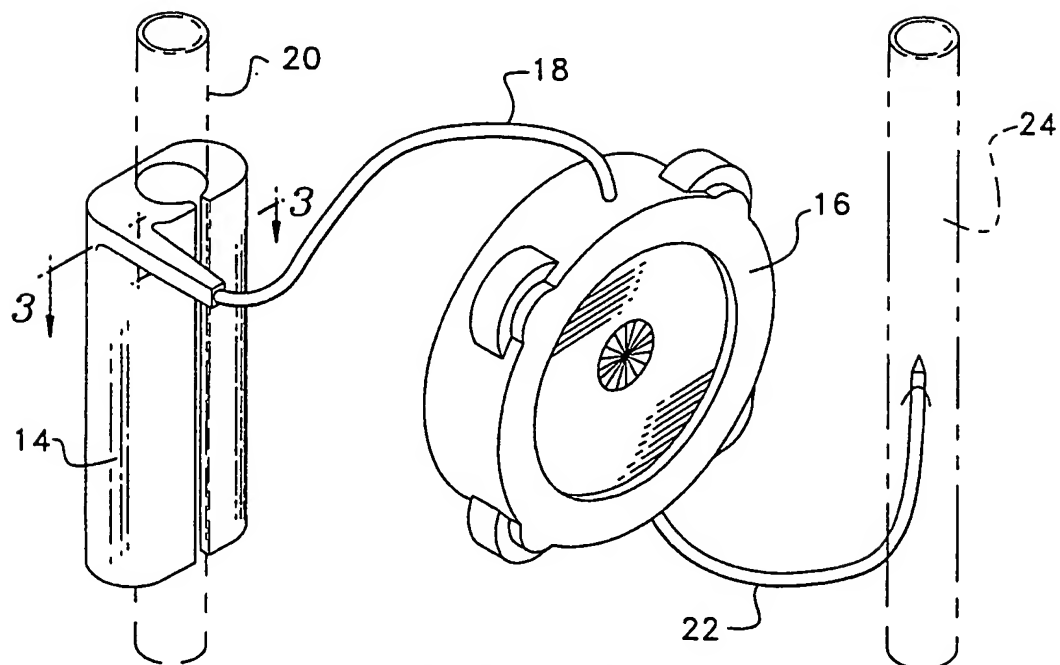
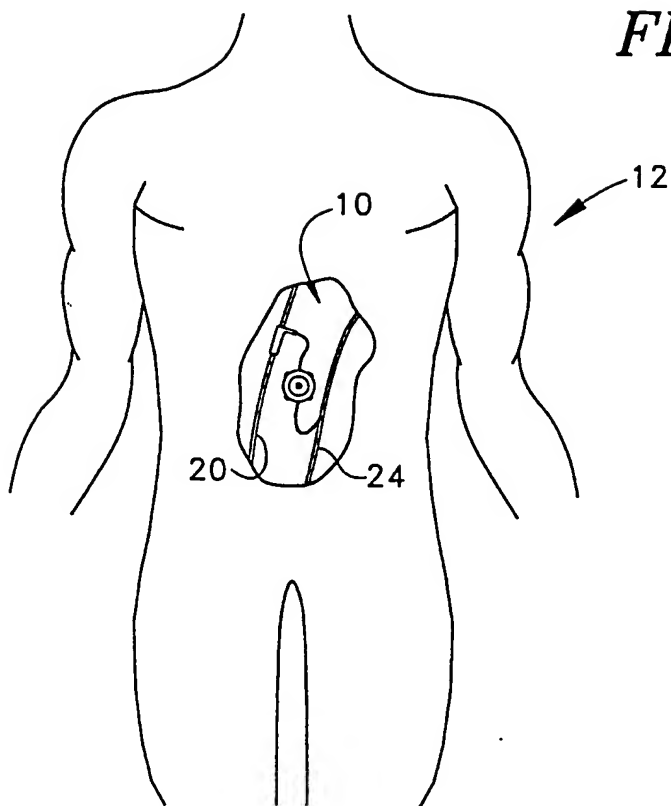
89. The device according to claim 89, wherein said insulin pump is located extracorporeally.

90. The device according to claim 89, wherein said insulin pump is implanted internally.

91. The device according to claim 74, wherein said selected band of radiation is substantially colinear to one another and interacts with substantially the same vascular tissue.

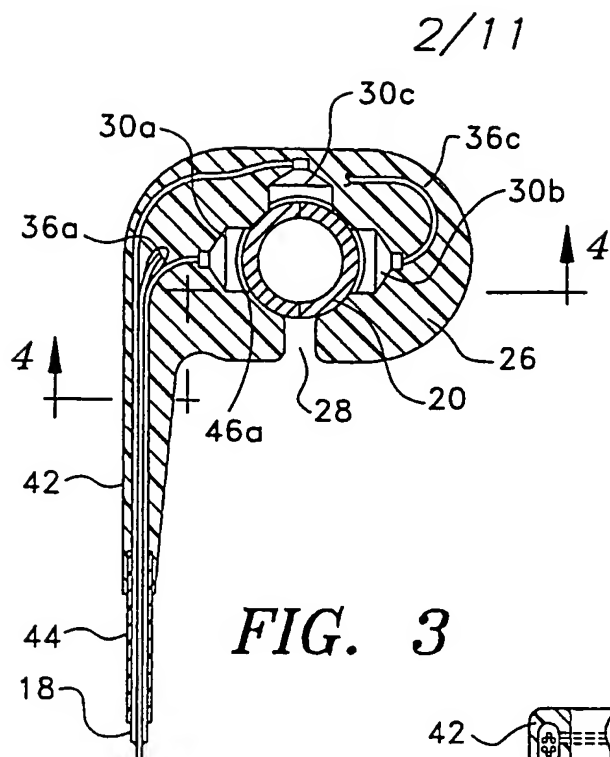
1/11

**FIG. 1**

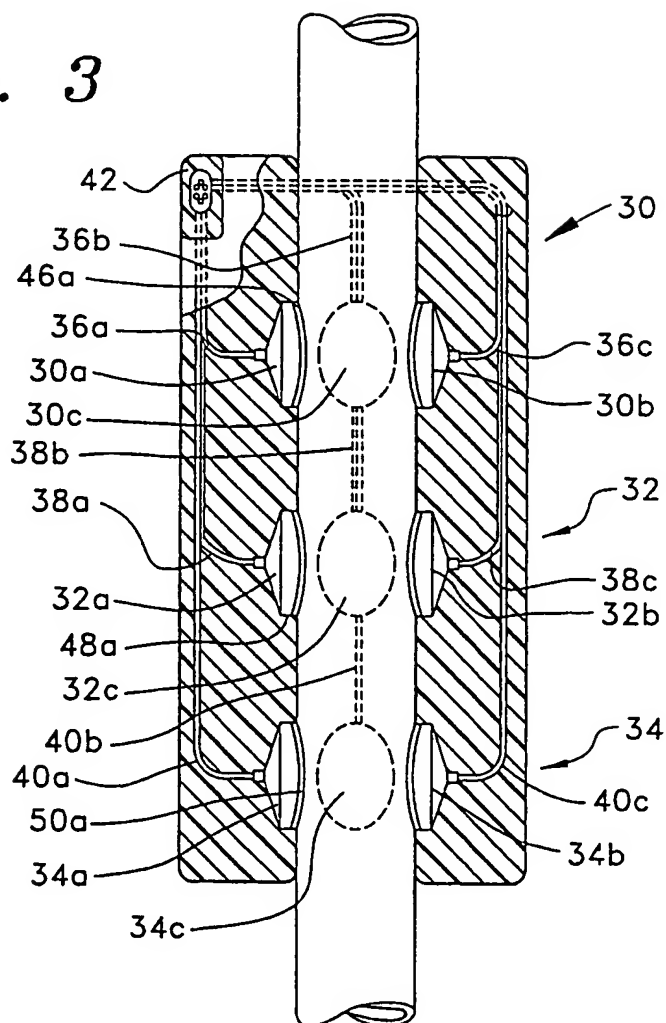


**FIG. 2**

SUBSTITUTE SHEET (RULE 26)



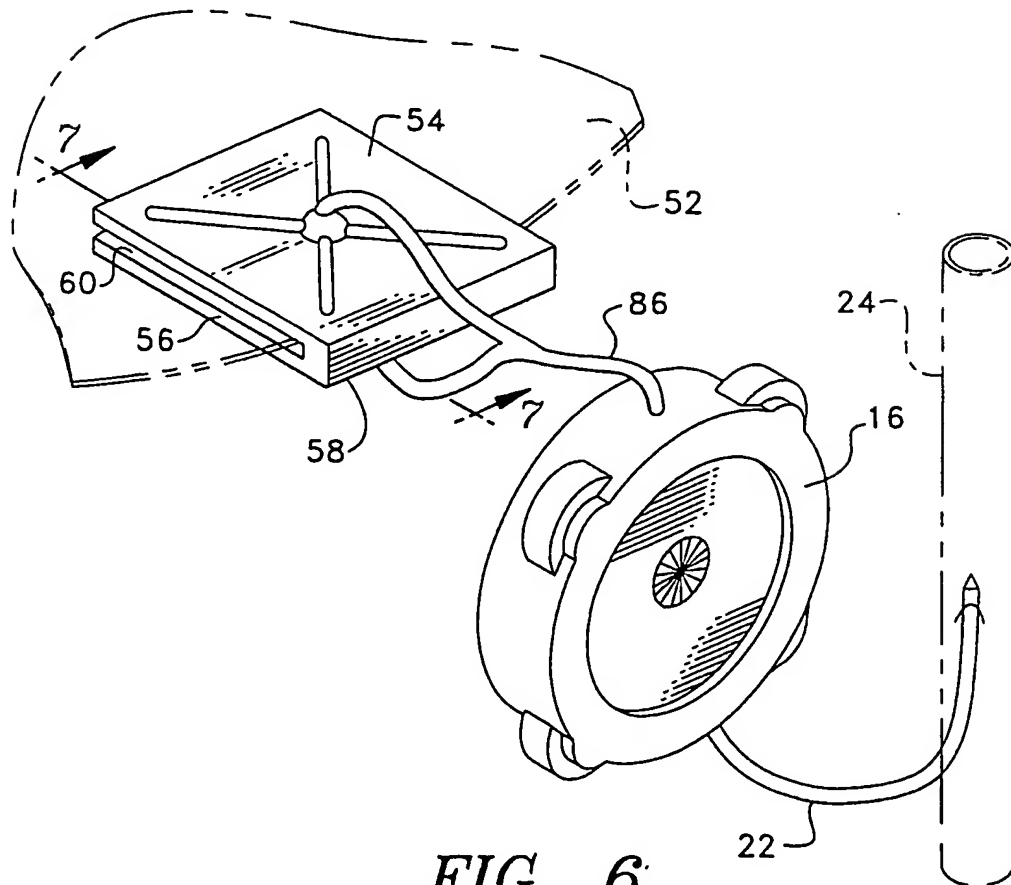
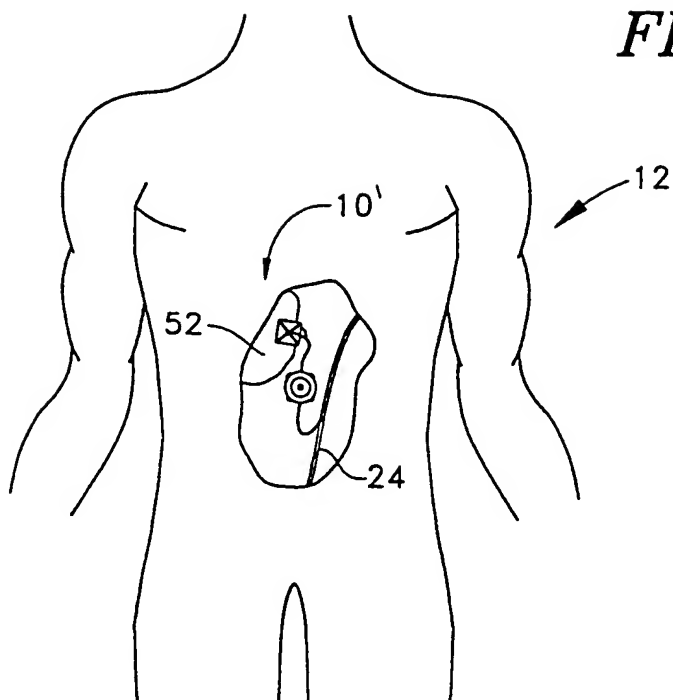
**FIG. 3**



**FIG. 4**

3/11

**FIG. 5**



**FIG. 6**



4/11

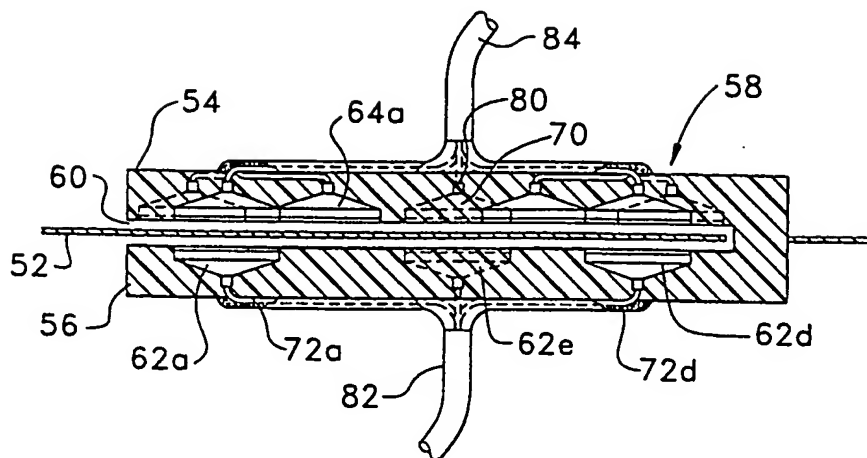


FIG. 7

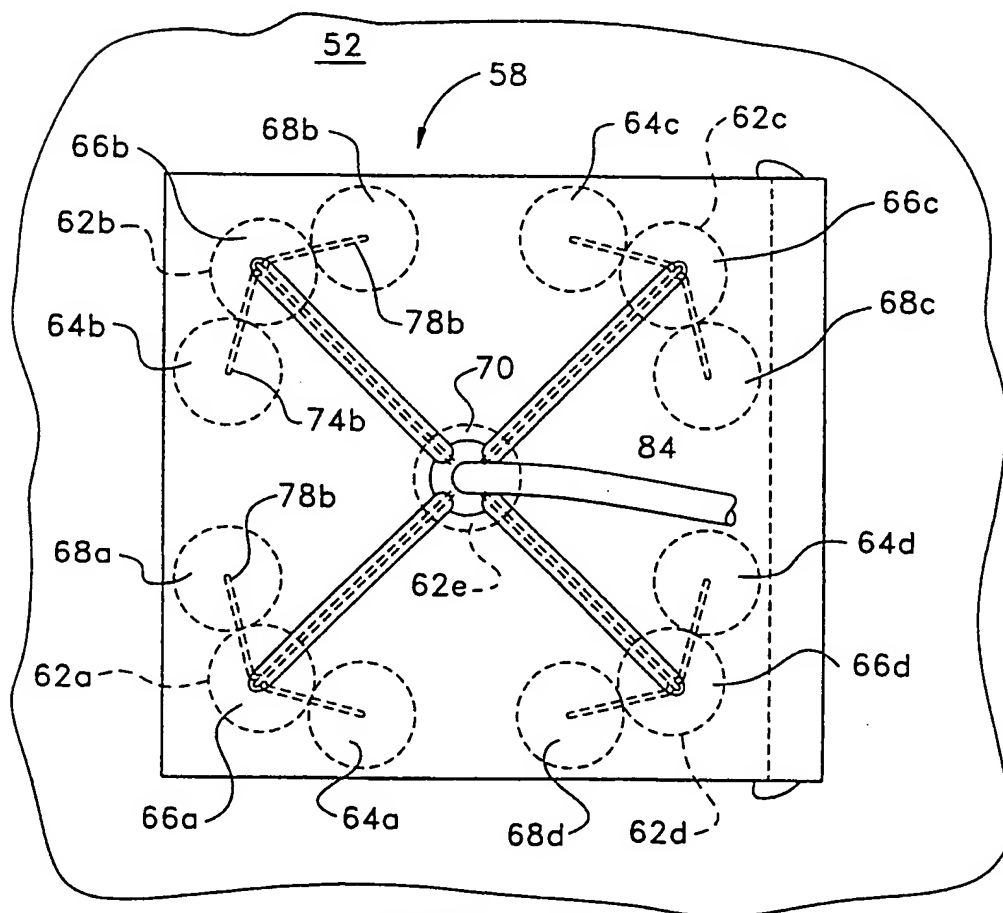
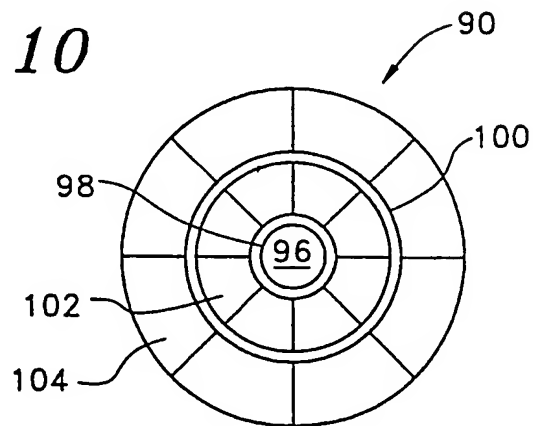
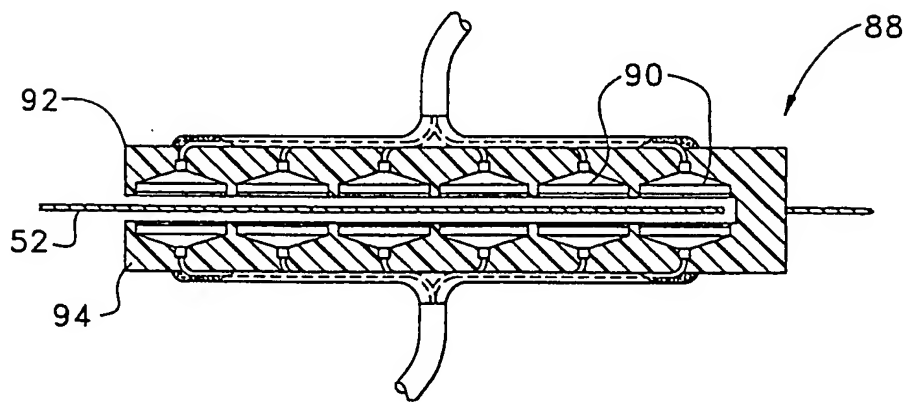
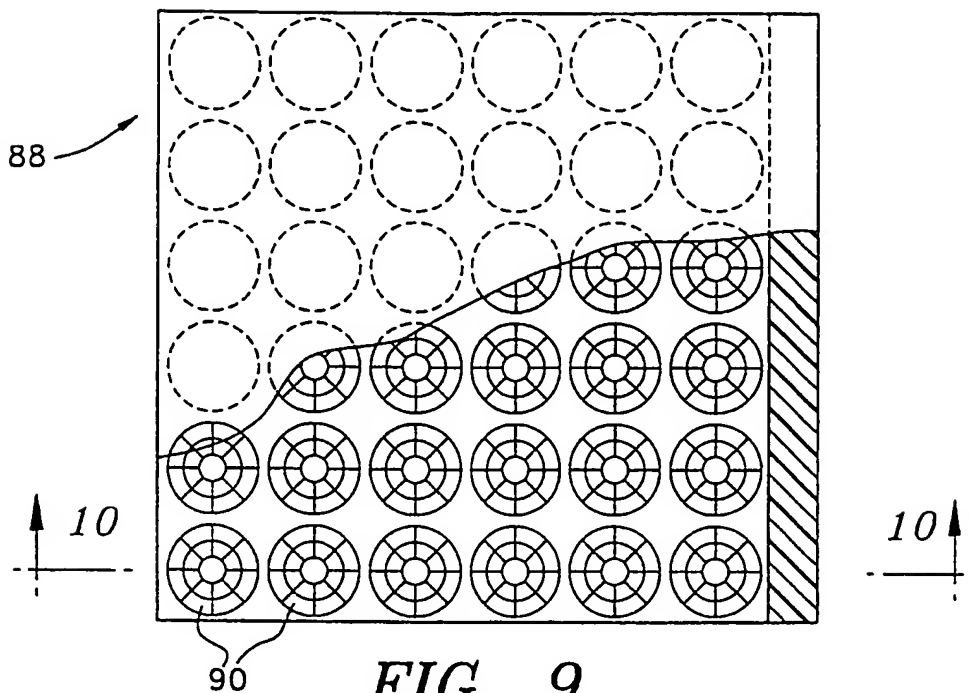


FIG. 8

5/11



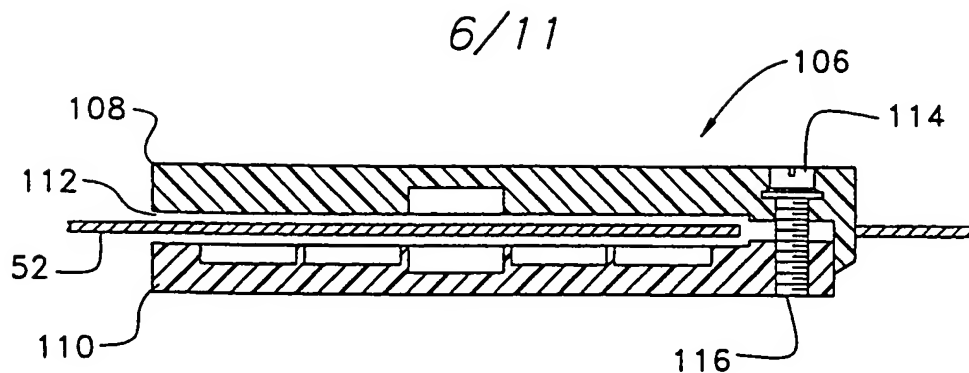


FIG. 12

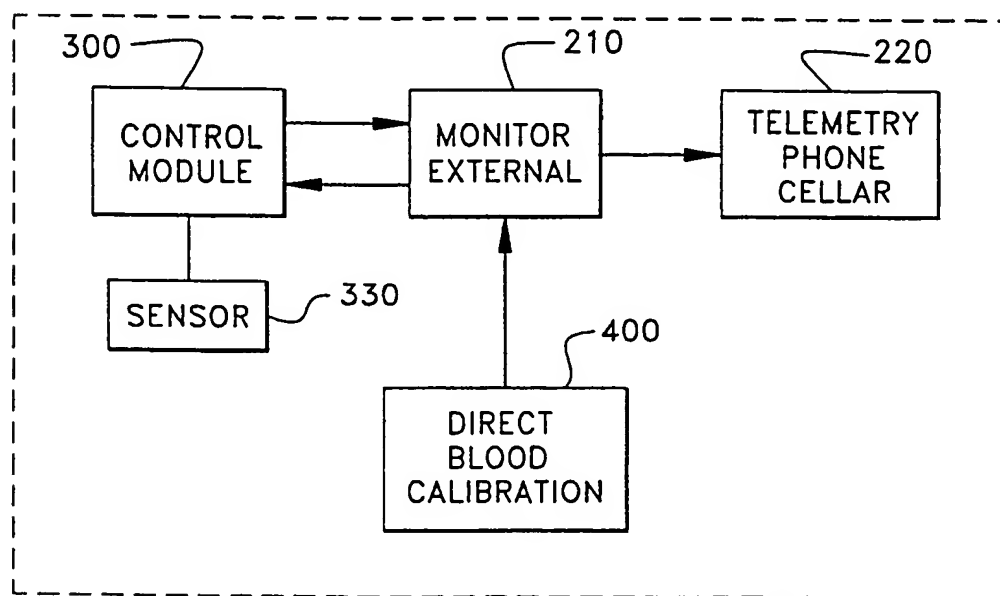


FIG. 13a

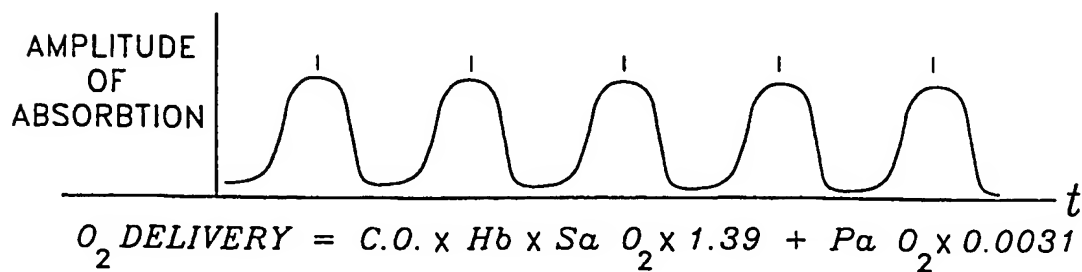
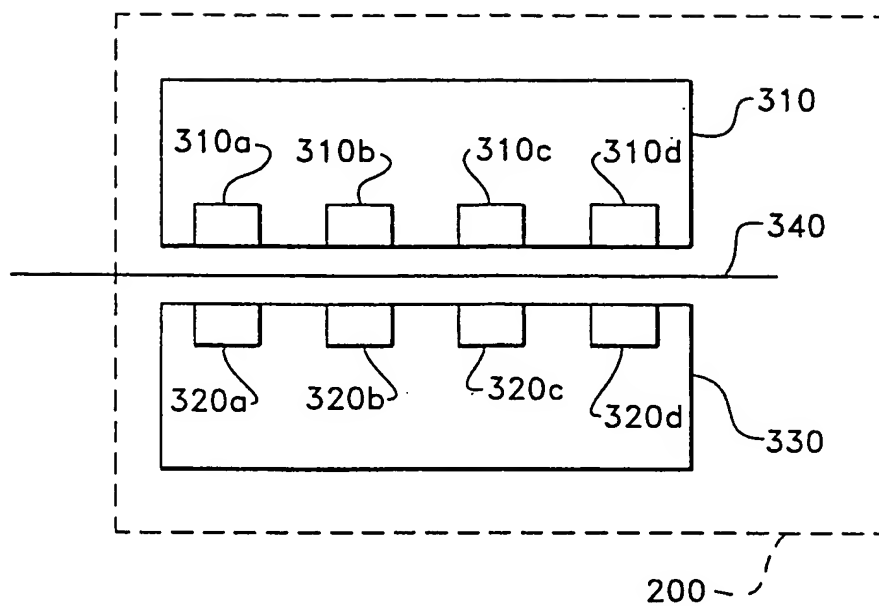
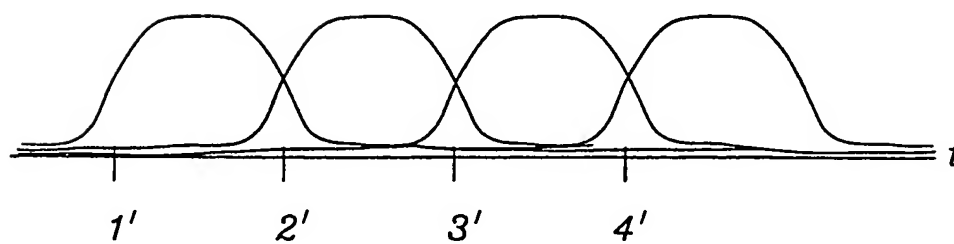


FIG. 13b

7/11

*FIG. 13C**FIG. 13d*

SUBSTITUTE SHEET (RULE 26)

8/11

FIG. 14

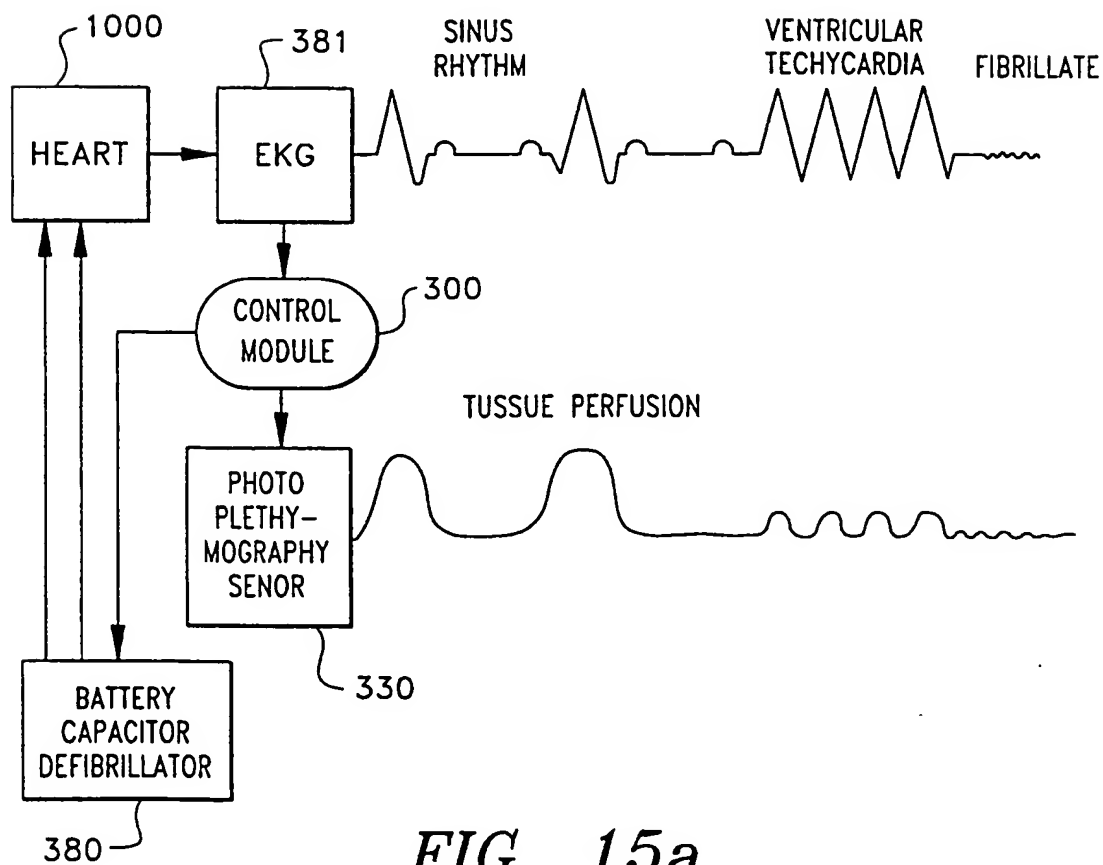
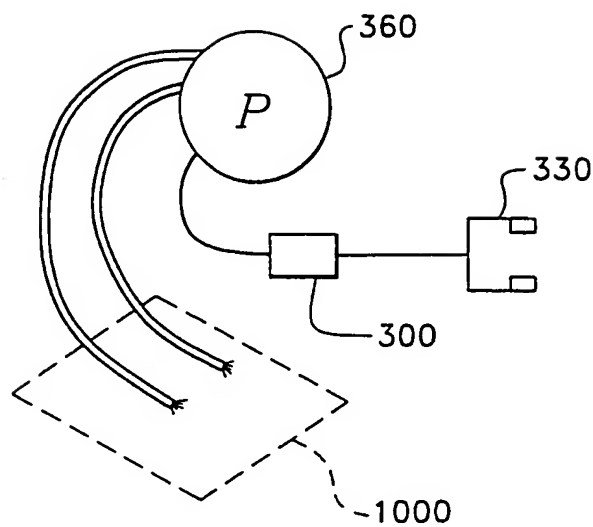
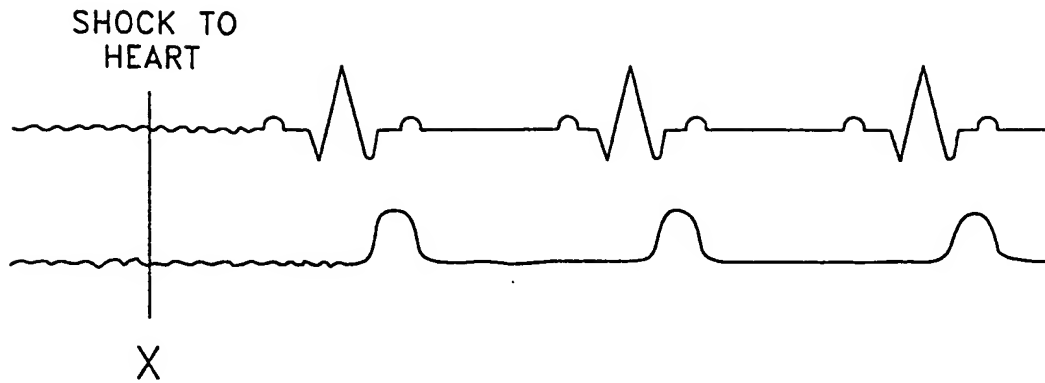
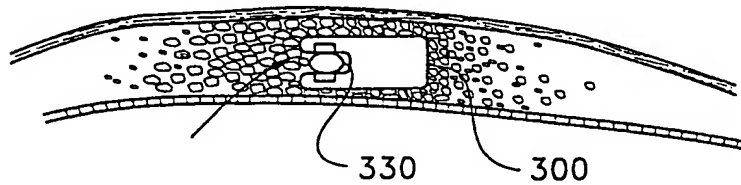
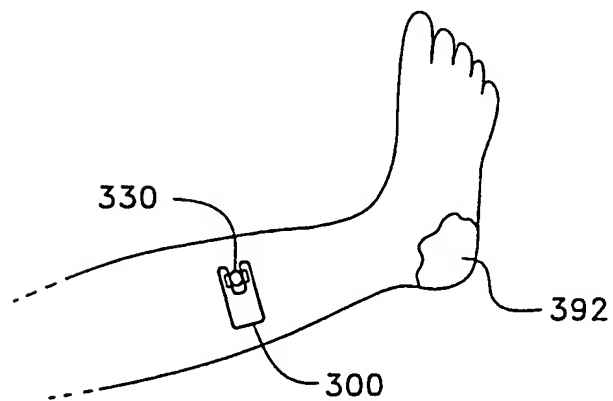


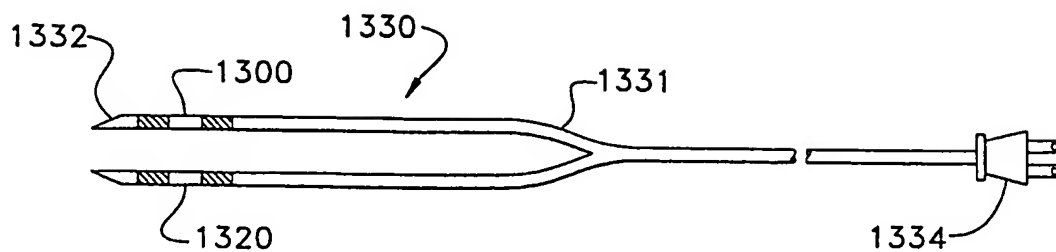
FIG. 15a

9/11

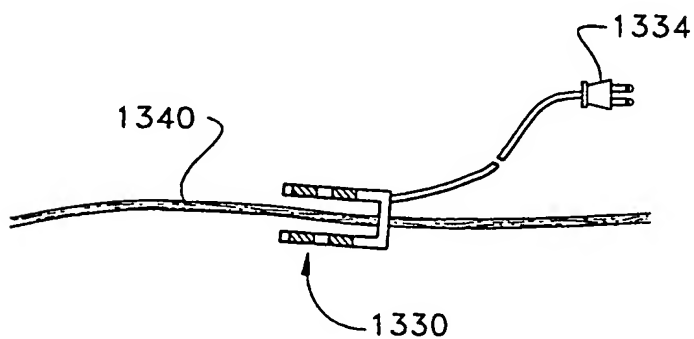
*FIG. 15b**FIG. 16a**FIG. 16b*

SUBSTITUTE SHEET (RULE 26)

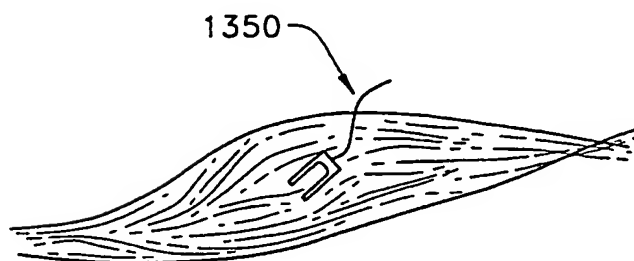
10/11



*FIG. 17a*



*FIG. 17b*



*FIG. 17c*

11/11

FIG. 18a

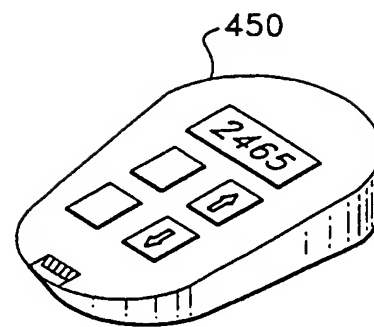
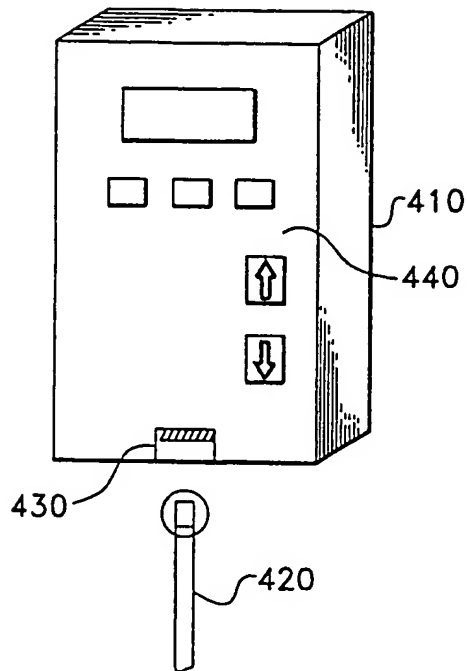


FIG. 18b

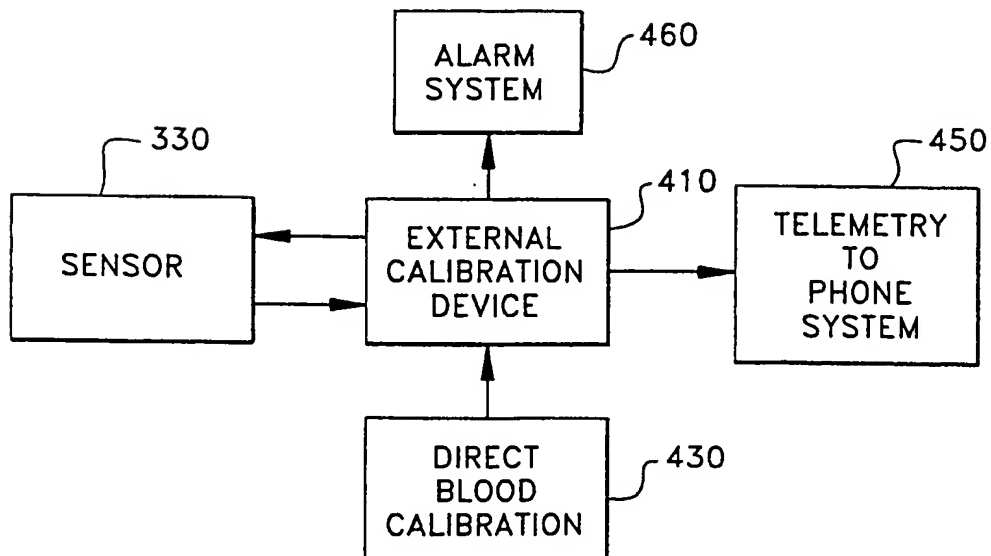


FIG. 18c



## INTERNATIONAL SEARCH REPORT

 International application No.  
 PCT/US96/11435

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61B 5/00

US CL : 128/633

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/633, 634; 356/39; 604/50, 66, 67, 890.1, 891.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,353,792 (LUBBERS ET AL.) 11 October 1994, see the entire document.	1, 12, 18-21, 27, 38, 46-49
Y, P	US, A, 5,474,552 (PALT) 12 December 1995, see the entire document.	18-21, 46-49
Y	US, A, 5,127,406 (YAMAGUCHI) 07 July 1992, see the entire document.	25, 26
Y	US, A, 4,865,038 (RICH ET AL) 12 September 1989, see the entire document.	25, 26
X --- Y	US, A, 4,807,629 (BAUDINO ET AL.) 28 February 1989, see column 1 lines 53-68, and column 3 lines 45-47.	57, 58, 60-64 ----- 59

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A		document defining the general state of the art which is not considered to be part of particular relevance
* E		earlier document published on or after the international filing date
* L		document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
* O		document referring to an oral disclosure, use, exhibition or other means
* P		document published prior to the international filing date but later than the priority date claimed
	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
	* Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
	* A	document member of the same patent family

Date of the actual completion of the international search

16 SEPTEMBER 1996

Date of mailing of the international search report

02 OCT 1996

 Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
 Box PCT  
 Washington, D.C. 20231

Facsimile No. (703) 305-3590

 Authorized officer *Diane L. Smith for*  
 ERIC F. WINAKUR

Telephone No. (703) 308-3940

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/11435

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US, A, 5,305,745 (ZACOUTO) 26 April 1994, see the entire document.	65-91 — 59